The American Journal of Medicine

1951

The American Journal of Medicine

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 19, N. Y. Yearly Subscription, $12.00 U. S. A.; $14.00 Canada and Latin American countries; $15.00 Foreign. Single Numbers $2.00; Special Numbers $4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. March, 1951—Volume X, No. 3. *Change of address must reach us one month preceding month of issue.*

new! penicillin + sulfonamides

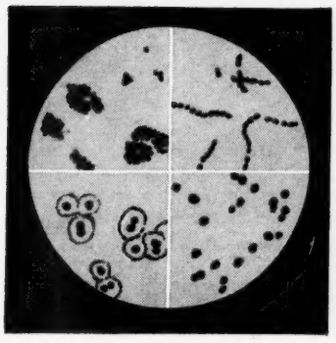
more rapid
more powerful
more effective

oral control of infection

mutually enhancing bacteriostasis

pentrisul

(PENICILLIN WITH TRIPLE SULFONAMIDES)



In PENTRISUL, penicillin is combined with sulfonamides for synergistic, mutually potentiating action against susceptible pathogenic organisms.

Certain bacteria resistant to penicillin succumb to the sulfonamides and vice versa . . . for more rapid, more effective bacteriostasis.

As contrasted with single sulfonamides, the greater solubility of sulfonamide mixtures practically eliminates the danger of renal damage from crystalluria.

each pentrisul tablet provides:

Potassium PENICILLIN-G	100,000 units
SULFADIAZINE	0.165 Gm.
SULFAMERAZINE	0.165 Gm.
SULFAMETHAZINE	0.165 Gm.

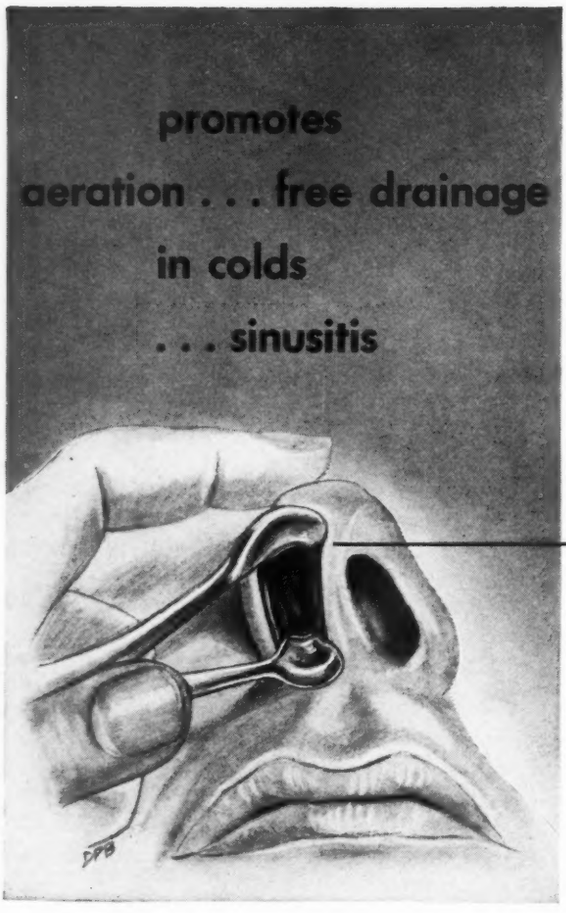
Bottles of 30, 100 and 500 Tablets

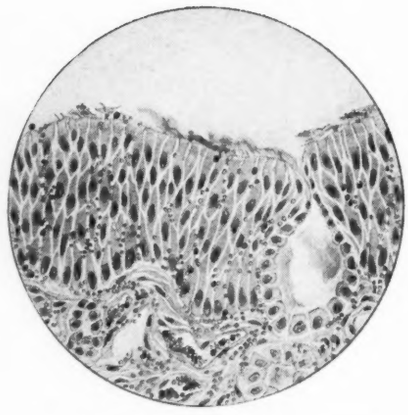
SAMPLES AND LITERATURE UPON REQUEST

CASIMIR **FUNK** LABORATORIES, INC.

affiliate of U. S. VITAMIN CORPORATION

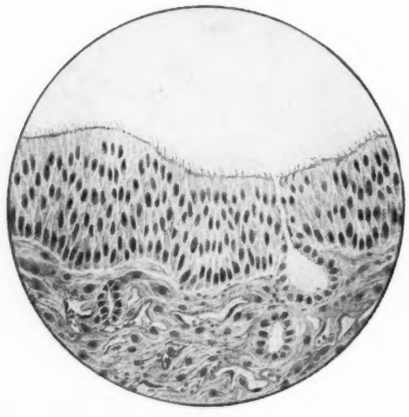
250 E. 43rd Street, New York 17, N.Y.





Nasal membrane showing increased leukocytes with denudation of cilia.

Normal appearing nasal epithelium.



Nasal engorgement and hypersecretion accompanying the common cold and sinusitis are quickly relieved by the vasoconstrictive action of

NEO-SYNEPHRINE®

HYDROCHLORIDE

Brand of Phenylephrine Hydrochloride

The decongestive action of several drops in each nostril usually extends over two to four hours. The effect is undiminished after repeated use.

Relatively nonirritating . . . Virtually no central stimulation.

Supplied in ¼% solution (plain and aromatic), 1 oz. bottles. Also 1% solution (when greater concentration is required), 1 oz. bottles, and ½% water soluble jelly, ⅝ oz. tubes.

Winthrop-Stearns INC.
NEW YORK 13, N. Y. WINDSOR, ONT.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Neo-Synephrine, trademark reg. U. S. & Canada

CONTENTS

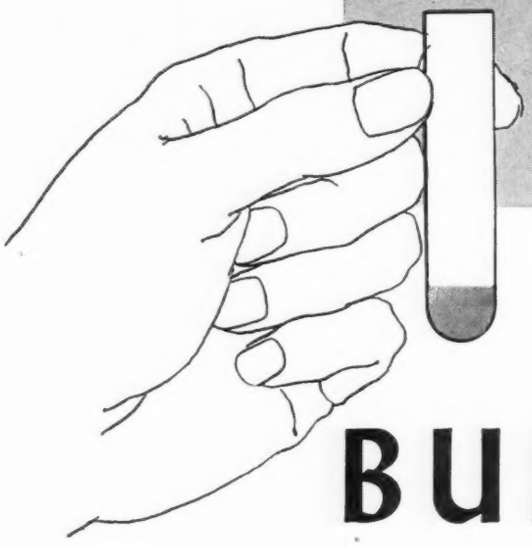
The American Journal of Medicine

VOL. X MARCH, 1951 NO. 3

Editorial

Clinical Studies

Contents continued on page 5



NEW

AMES DIAGNOSTIC REAGENT TABLET

BUMINTEST

for detection of albumin in urine

For office, laboratory or bedside determination of clinically significant albuminuria, *Bumintest* (Brand) Reagent Tablets have these advantages:

test is quick • noncaustic-noncorrosive

no heat required • inexpensive

reliable

A modification of the well-established sulfosalicylic acid method, the amount of albumin present is estimated by the degree of turbidity.

For the rapid and more convenient performance of basic diagnostic tests without heating or special equipment, *Bumintest* (Brand) Reagent Tablets now join

ACETEST for detection of acetone
CLINITEST for detection of urine-sugar
HEMATEST for detection of occult blood

Acetest, Bumintest, Clinitest, Hematest, Reg. Trademarks.

AMES

AMES COMPANY, INC • ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

CONTENTS

The American Journal of Medicine

VOL. X MARCH, 1951 NO. 3

Contents continued from page 3

Contents continued on page 7

"...the only drug we have seen that allays anxiety without clouding consciousness"

J.A.M.A. *140*:672 (June 25) 1949

Tolserol *(Squibb Mephenesin)*

- **to alleviate pronounced anxiety and tension**
- **as an adjunct in the treatment of chronic alcoholics**

DOSAGE

In anxiety tension states:

As little as 0.5 Gm., given orally every few hours, has produced a good response. However, for optimum effect, 0.75 Gm. or more is given several times a day.

As an adjunct in the treatment of chronic alcoholics:

As much as 3 Gm. orally every four hours has been found useful in the acute stage. This dosage is reduced when the patient becomes more manageable. (If Tolserol is given too soon after the patient drank alcohol, the toxic effect of the alcohol may be potentiated. For this reason, Tolserol should not be administered until six hours have elapsed since the patient drank alcohol.)

Tablets, 0.5 Gm., 0.25 Gm.; *Capsules*, 0.25 Gm.;
Elixir, 0.1 Gm. per cc.; *Solution*, 2% (intravenous).

Tolserol *(Squibb Mephenesin)*

SQUIBB 745 FIFTH AVENUE, NEW YORK 22, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

CONTENTS

The American Journal of Medicine

VOL. X MARCH, 1951 NO. 3

Contents continued from page 5

Clinic on Psychosomatic Problems

Clinico-pathologic Conference

Case Report

Change of address must reach us one month preceding month of issue.

for keeping cardiacs edema-free

Effective and well tolerated, Tablets MERCUHYDRIN with Ascorbic Acid are unexcelled for diuretic maintenance therapy.

Continuous administration of one or two Tablets MERCUHYDRIN with Ascorbic Acid daily—plus an occasional injection of MERCUHYDRIN Sodium—keep the average cardiac free of edema.

Because "maximum absorption occurs relatively high in the gastrointestinal tract (stomach and duodenum)"* Tablets MERCUHYDRIN with Ascorbic Acid are simple sugar-coated. Unlike poorly tolerated oral mercurials—which require enteric coating—clinical experience has shown that these sugar-coated tablets produce dependable diuresis with minimal side effects.

tablets

MERCUHYDRIN®

(brand of meralluride)

with ascorbic acid

the simplest method of outpatient maintenance

To secure the greatest efficacy and *all* the advantages of Tablets MERCUHYDRIN with Ascorbic Acid, a three-week initial supply should be prescribed . . . 25 to 50 tablets. Available in bottles of 100 simple sugar-coated tablets each containing meralluride 60 mg. (equivalent to 19.5 mg. of mercury) and ascorbic acid 100 mg.

*Overman, W. J.; Gordon, W. H., and Burch, G. E.: Tracer Studies of the Urinary Excretion of Radioactive Mercury following Administration of a Mercurial Diuretic, Circulation *1*:496, 1950.

Lakeside Laboratories, INC., MILWAUKEE 1, WISCONSIN

Problem Patient

bald, bearish, and bloated . . .

BILLINGSWORTH BLUECHIP bustles and burps from one big deal to another, mingling mergers with bluepoints and bourbon and proxies with Pilsener and mutton pot pie.

Between times, Mr. Bluechip huffs and puffs at his board of directors, and grumbles of gas on the stomach.

In other words, old B. B. is just like a million other business bigwigs who know all about capital assets and obsolescence, except as applied to the epigastrium. They don't feel sick, but they don't feel well — and they aren't going to feel any better as long as they cherish their foibles and follies and mock the mandate of mellowing years to mend their ways at the table.

There's no one way to handle the Billingsworth Bluechips and their willful adherence to habit. But it's said that "the commonest cause" of digestive distress in patients over forty is low grade biliary dysfunction. And such being the case, DEPANCOL will often serve an important two-fold purpose: (1) To afford prompt relief from the classic complaints — flatulence, bloating, dyspepsia, etc. — thus encouraging the patient's early cooperation in a long-range corrective program; and (2) To flush and activate the sluggish biliary system, thus encouraging restoration of normal function by physiologic means.

Depancol®

Dehydrocholic Acid	⅓ gr.
Bile Salts	1½ gr.
Pancreatic substance equivalent to Pancreatin U.S.P.	4½ gr.

in an enteric coated tablet

Note: no laxatives

SUPPLY Bottles of 50, 500, and 5,000 enteric coated tablets, available at your druggist.

DOSAGE Average: 1 or 2 tablets 3 times daily, with or after meals.

CHILCOTT *Laboratories*

DIVISION OF The Maltine Company

MORRIS PLAINS, NEW JERSEY

BOOK SECTION

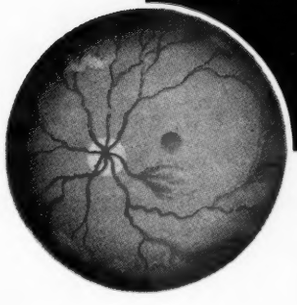
"We have not read an author till we have seen his object, whatever it may be, as he saw it."

—Carlyle

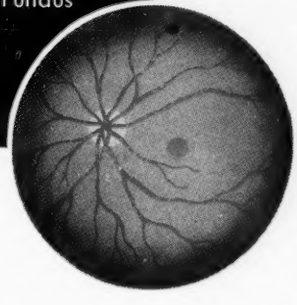
RUTAMINAL*

the protection of **rutin**[1] the action of **aminophylline** the sedation of **phenobarbital** —for use in selected cardiovascular and diabetic conditions in which excessive capillary fragility presents a complicating hazard —bottles of 100 tablets

Ocular Fundus in Degenerative Vascular Disease—Hypertension, Diabetes, Arteriosclerosis —note tortuous blood vessels, areas of exudation, hemorrhagic areas.



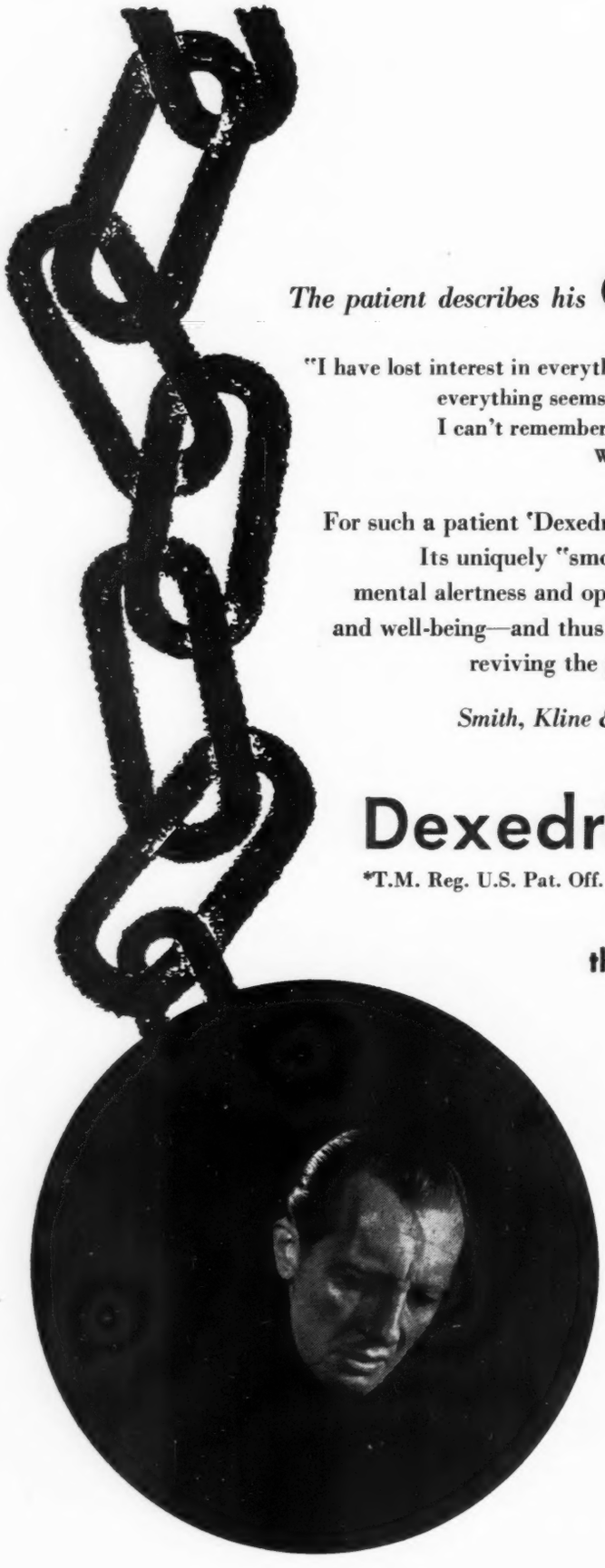
Normal Ocular Fundus



[1]In keeping with newer clinical findings, the rutin content of RUTAMINAL has been increased to 60 mg. per tablet (three times the former rutin content) at no increase in cost to the patient.

*RUTAMINAL is the trademark of Schenley Laboratories, Inc. and designates exclusively its brand of tablets containing rutin, aminophylline, and phenobarbital.

schenley laboratories, inc., 350 fifth ave., new york 1, n. y.



The patient describes his **depression:**

"I have lost interest in everything—I have no ambition any more—
everything seems futile—I feel frustrated and lonely—
I can't remember or concentrate—I am *all slowed up*."
Washburne, A.C.: Ann. Int. Med. *32*:265, 1950.

For such a patient 'Dexedrine' Sulfate is of unequalled value. Its uniquely "smooth" antidepressant effect restores mental alertness and optimism, induces a feeling of energy and well-being—and thus has the happy effect of once again reviving the patient's interest in life and living.

Smith, Kline & French Laboratories, Philadelphia

Dexedrine* Sulfate

*T.M. Reg. U.S. Pat. Off.

the antidepressant of choice

tablets

elixir

...A Complete Response *in* HYPERTENSION

THE BLOOD PRESSURE DROPS

Through reduction of peripheral resistance, Veriloid produces a significant drop in arterial tension. Not only is that large group of patients with moderate hypertension benefited, but also patients with severe essential and malignant hypertension. The average dose of from 2.0 to 5.0 mg. four times daily after meals and at bedtime usually suffices, although individualization of dosage is essential for maximum therapeutic efficacy and avoidance of nausea.

THE PATIENT IMPROVES SUBJECTIVELY

The gratifying feature of Veriloid therapy is the speed with which the distressing discomfort of hypertension is overcome. Headache disappears, easy fatigability lessens, vision has been reported to improve through absorption of retinal exudations, and kidney function is increased. These beneficial changes, often experienced before the blood pressure has dropped significantly, are presumably related to the vasorelaxation induced by Veriloid and the resulting improved tissue nutrition. Literature available on request.

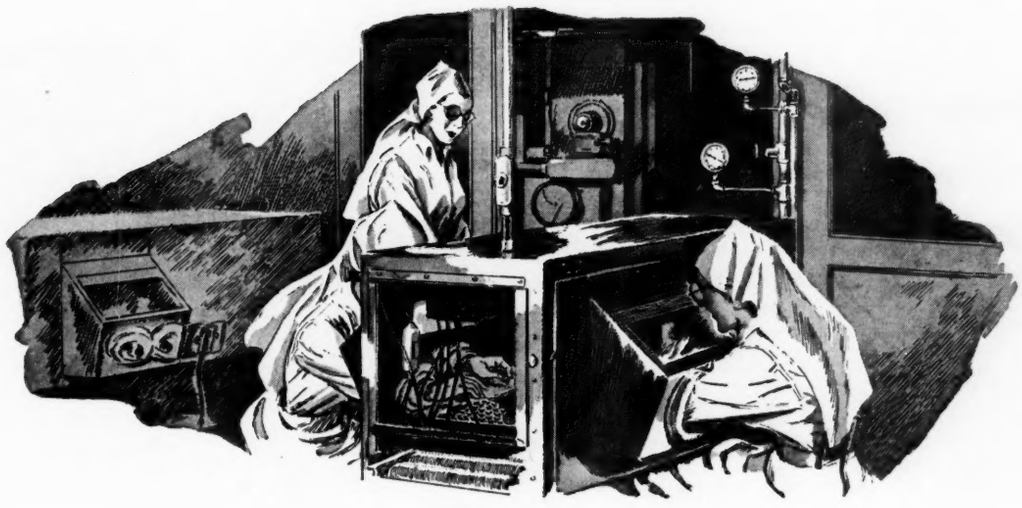
VERILOID*
Now Available in 3 Tablet Sizes

Veriloid, a unique biologically standardized fraction of Veratrum viride, is now available in 3 dosage units for maximum economy —1 mg., 2 mg., and 3 mg. tablets; bottles of 100, 500, and 1000.

*T. M. OF RIKER LAB., INC.

RIKER LABORATORIES, INC.
8480 BEVERLY BLVD., LOS ANGELES 48, CALIF.

VERILOID
A PRODUCT OF RIKER RESEARCH



AUREOMYCIN

Hydrochloride Crystalline

Lederle

Effective against many bacterial and rickettsial infections, as well as certain protozoal and large viral diseases

Every precaution against contamination and every device that will safeguard the quality and sterility of the content of aureomycin in vials for research parenteral use has been adopted in the sterile filling rooms at our Pearl River laboratories. Rigid aseptic technique surrounds the filling process. The actual filling takes place in a stainless steel tunnel equipped with ultraviolet lights. No human hand takes part at any stage, until the plugs are inserted in the vials. Plugging is done inside an ultraviolet irradiated chamber with only the sterile-gloved hand of the operator inside.

Aureomycin is now available in a number of convenient forms, for use locally and by mouth. New forms of this antibiotic of unsurpassed versatility are constantly being perfected.

Capsules: *Bottles of 25, 50 mg. each capsule. Bottles of 16, 250 mg. each capsule.*
Ophthalmic: *Vials of 25 mg. with dropper; solution prepared by adding 5 cc. of distilled water.*

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY 30 Rockefeller Plaza, New York 20, N.Y.

IN UPPER RESPIRATORY INFECTIONS

prompt response

in acute laryngotracheal bronchitis

CASE	DIAGNOSIS	INFECTING ORGANISM	DAYS TREATED	TOTAL DOSE GM.	ADMINISTRATION	CONDITION AND RESULT
16	Acute laryngo-tracheal bronchitis	Hemophilus influenzae	3	12	oral	Marked improve-ment in 24 hours. Recovery

Case report taken from Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Ann. New York Acad. Sc. 53:448 (Sept. 15) 1950.

CRYSTALLINE

Terra

prompt response

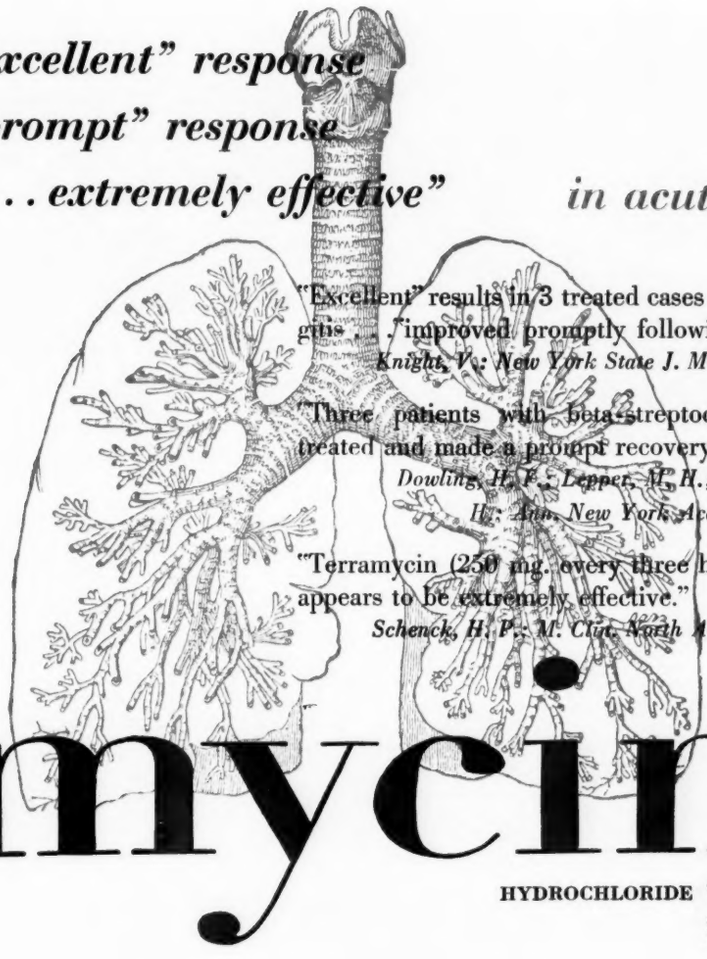
in acute follicular tonsillitis

CASE	DIAGNOSIS	CULTURE		DAILY DOSE GM.	NUMBER OF DAYS TREATED	RESULT
		SOURCE	ORGANISM			
29	Acute follicular tonsillitis	throat	Strepto-coccus pyogenes	4	3	Prompt clinical response. No fever after 24 hours of treatment

Case report taken from Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet., Mayo Clin. 25:183 (Apr. 12) 1950.

Antibiotic Division **Pfizer**

"excellent" response
"prompt" response
"... extremely effective" *in acute pharyngitis*



"Excellent" results in 3 treated cases of streptococcic pharyngitis . . . "improved promptly following terramycin therapy."
Knight, V.: New York State J. Med. 50:2173 (Sept. 15) 1950.

"Three patients with beta-streptococcic pharyngitis were treated and made a prompt recovery."
Dowling, H. F., Lepper, M. H.; Caldwell, E. R., and Spies, H.: Ann. New York Acad. Sc. 53:433 (Sept.) 1950.

"Terramycin (250 mg. every three hours) when given orally appears to be extremely effective."
Schenck, H. P.: M. Clin. North America 34:1621 (Nov.) 1950.

mycin

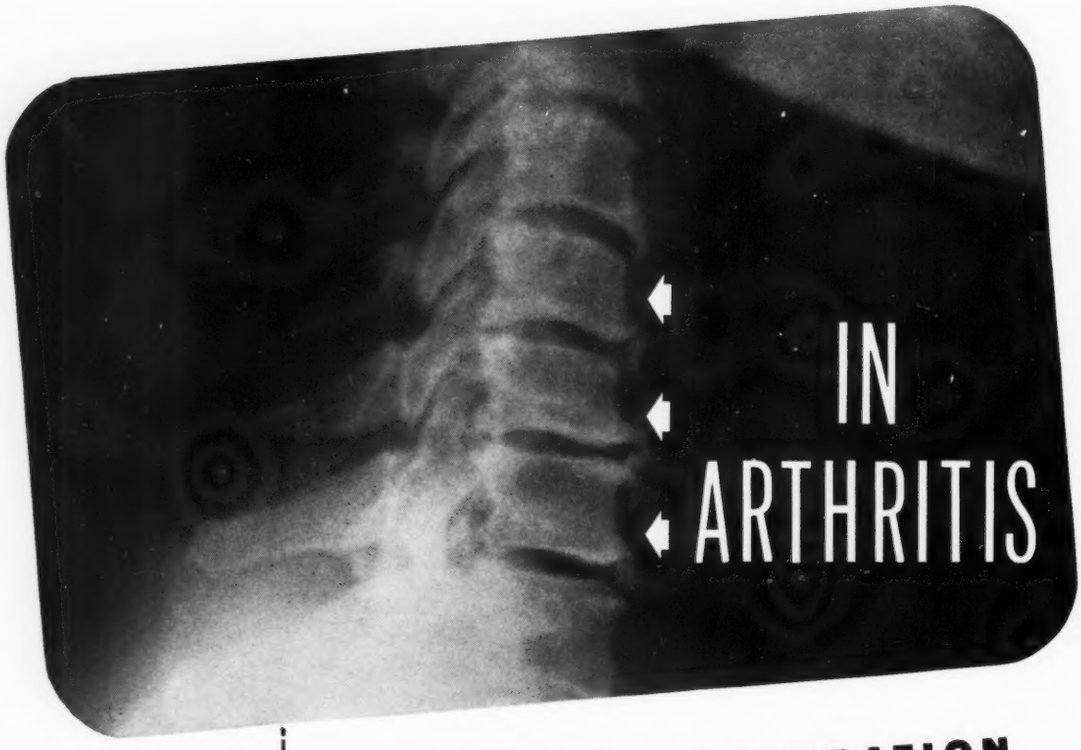
HYDROCHLORIDE

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Dosage: On the basis of findings obtained in over 150 leading medical research centers, 2 Gm. daily by mouth in divided doses q. 6 h. is suggested for most acute infections. In severe infections a high initial dose (1 Gm.) or higher daily doses (3 to 6 Gm.) should be used. Treatment should be continued for at least 48 hours after the temperature is normal and acute symptoms subside.

Supplied: 250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*



COMPLETE SALICYLATE SATURATION

Without side effects

Relief of arthritic pain, the objective of therapy in joint involvements, is readily achieved with Salcedrox. The buffered sodium salicylate is more easily tolerated than salicylate alone, and is rendered systemically less toxic by the presence of calcium. The tendency to increased ascorbic acid loss is counteracted by the presence of calcium ascorbate in Salcedrox.

Salcedrox is highly useful whenever salicylates are indicated —in arthritis, rheumatoid involvements, neuromuscular affections, and rheumatic fever. It is available on prescription at all pharmacies. Literature supplied on request.

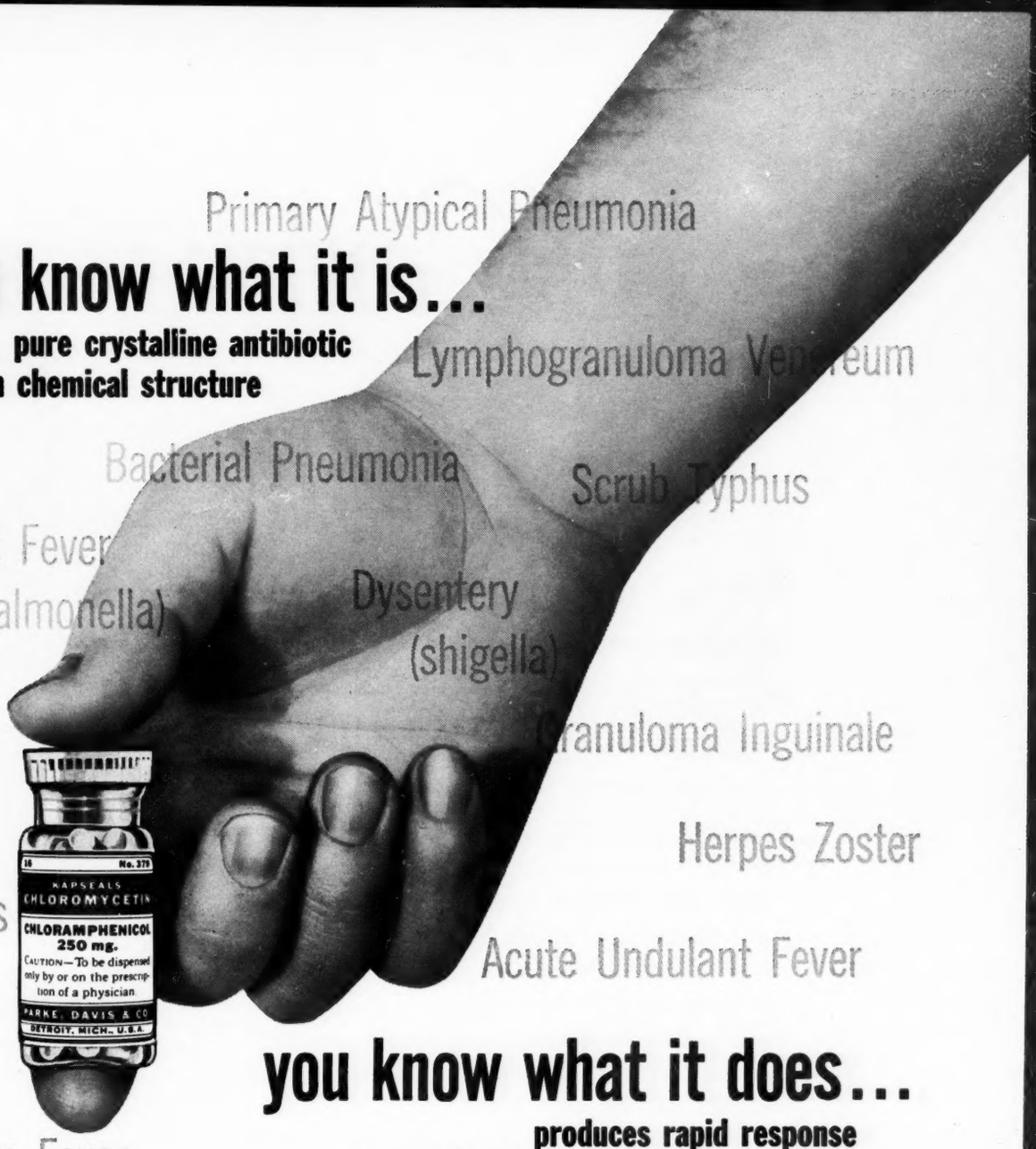
SE M CO

Each Salcedrox tablet supplies:

Sodium salicylate	5 gr.
Aluminum hydroxide gel, dried	2 gr.
Calcium ascorbate (equivalent to 50 mg. of ascorbic acid)	1 gr.
Calcium carbonate	1 gr.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

SALCEDROX
TABLETS



you know what it is...

pure crystalline antibiotic of known chemical structure

you know what it does...

produces rapid response in a wide range of infectious diseases

Chloromycetin®

Chloramphenicol, Parke-Davis

Supplied in Kapseals® of 250 mg., and in capsules of 50 mg.

PARKE, DAVIS & COMPANY

MEDICAMENTA VERA · P D & CO.

Cortone®

Saline Suspension of CORTONE Acetate

(1 cc. = 25 mg.) vials, 20 cc.

Tablets— CORTONE Acetate

(25 mg. each) bottles, 40 tablets

Clinical studies have demonstrated that the therapeutic activity of Cortone* is similar whether administered parenterally or orally. Dosage requirements are approximately the same, and the two routes of administration may be used interchangeably or additively at any time during treatment.

Although the manufacture of Cortone—probably the most intricate and lengthy synthesis ever undertaken—has imposed unprecedented difficulties, every effort is being made to increase production and, in the meantime, to achieve an equitable national distribution of this vital drug.

Literature on Request

Key to a New Era in Medical Science

Cortone®

ACETATE

(CORTISONE Acetate Merck)

(11-Dehydro-17-hydroxycorticosterone-21-acetate)

Among the conditions in which Cortone has produced striking clinical improvement are:

RHEUMATOID ARTHRITIS and Related Rheumatic Diseases

ACUTE RHEUMATIC FEVER

ALLERGIC DISORDERS, including Bronchial Asthma

INFLAMMATORY EYE DISEASES

SKIN DISORDERS, notably Atopic Dermatitis, Psoriasis, Exfoliative Dermatitis, including cases secondary to drug reactions, and Pemphigus

LUPUS ERYTHEMATOSUS (Early)

ADDISON'S DISEASE

**CORTONE is the registered trade-mark of Merck & Co., Inc. for its brand of cortisone.*

MERCK & CO., INC.

Manufacturing Chemists

RAHWAY, NEW JERSEY

Ammivin is pure khellin. This new weapon against angina pectoris and coronary insufficiency offers these advantages:

Ammivin is approximately five times as potent a vasodilator as aminophylline.

Ammivin is selective. Dilates the coronary arteries without appreciable effect on peripheral circulation—does not alter blood pressure •

Each ***Ammivin*** tablet contains 20 mg. of khellin to allow flexibility of dosage •

Ammivin is enteric coated •

Ammivin is the preferred dosage form of khellin •

How Supplied: Bottles of 40 and 100 tablets.

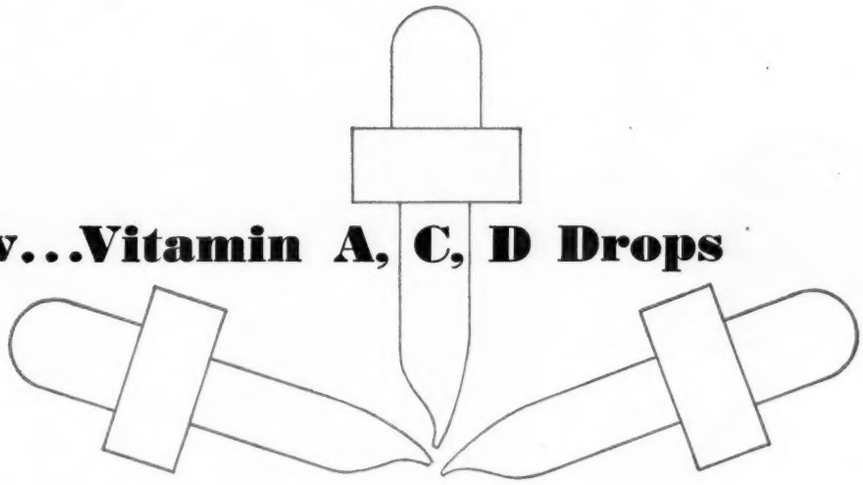
Comprehensive Brochure upon request.

Ammivin

(pure khellin)

a potent coronary vasodilator

The National Drug Company,
Philadelphia 44, Pa.
More than Half a Century
of Service to the Medical Profession



Now...Vitamin A, C, D Drops

in aqueous solution  **for *better absorption***

Aquasperse

Vitamin ACD Drops

Advantages:

Aqueous Solution—means faster and more efficient absorption of the fat-soluble vitamins A and D.

In conditions in which fat absorption is impaired, such as diarrheas, celiac disease, hepatic and biliary disturbances, the value of an aqueous solution is obvious.

Hypoallergenic—all the component vitamins of Aquasperse are synthetic. Consequently it may be used where patients cannot tolerate natural source vitamins.

Pleasant flavor . . . no objectionable odor—Aquasperse has an appealing, slightly citrus flavor and practically no odor.

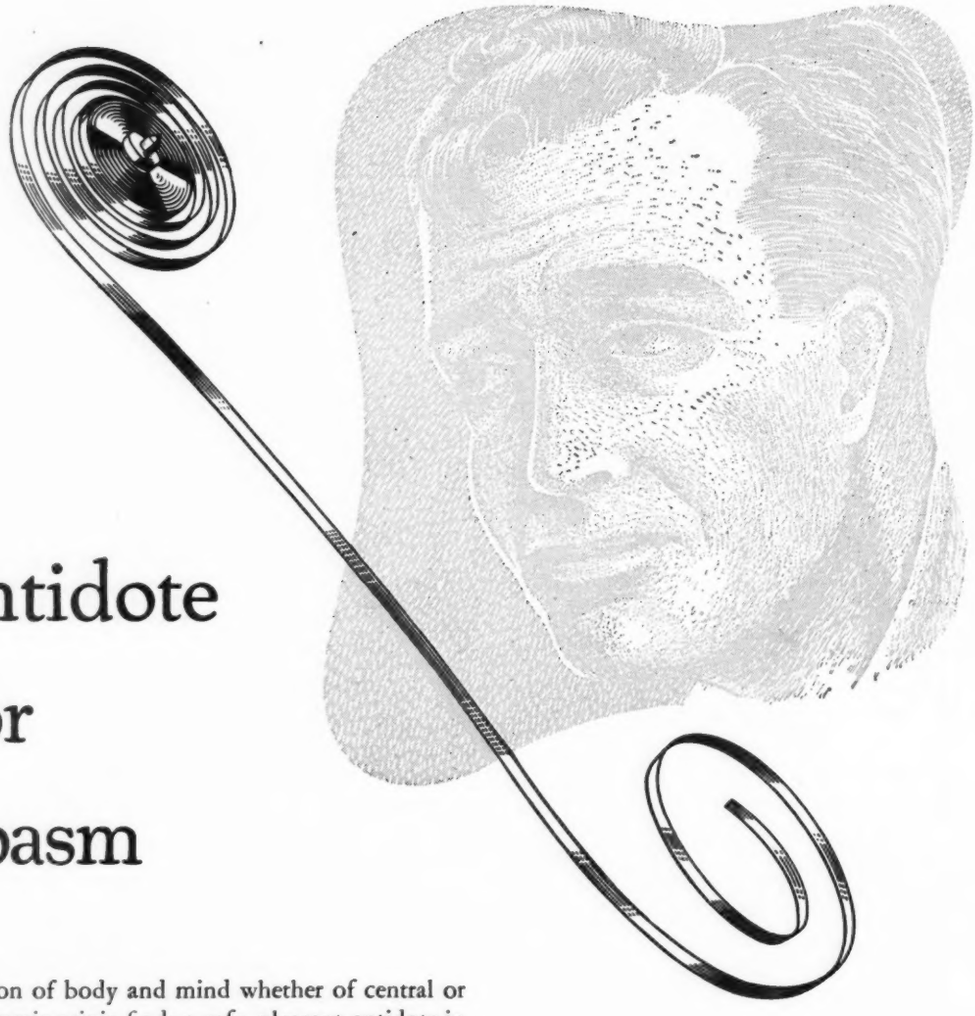
EACH 0.6 CC. CONTAINS:

vitamin A	5000 U.S.P. Units
vitamin D_3	1000 U.S.P. Units
ascorbic acid	50 mg.

Note: The vitamin D_3 in Aquasperse is chemically identical and biologically equivalent to the vitamin D of cod liver oil.

Available—In bottles of 15 cc. and 50 cc. (with calibrated dropper)

WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.



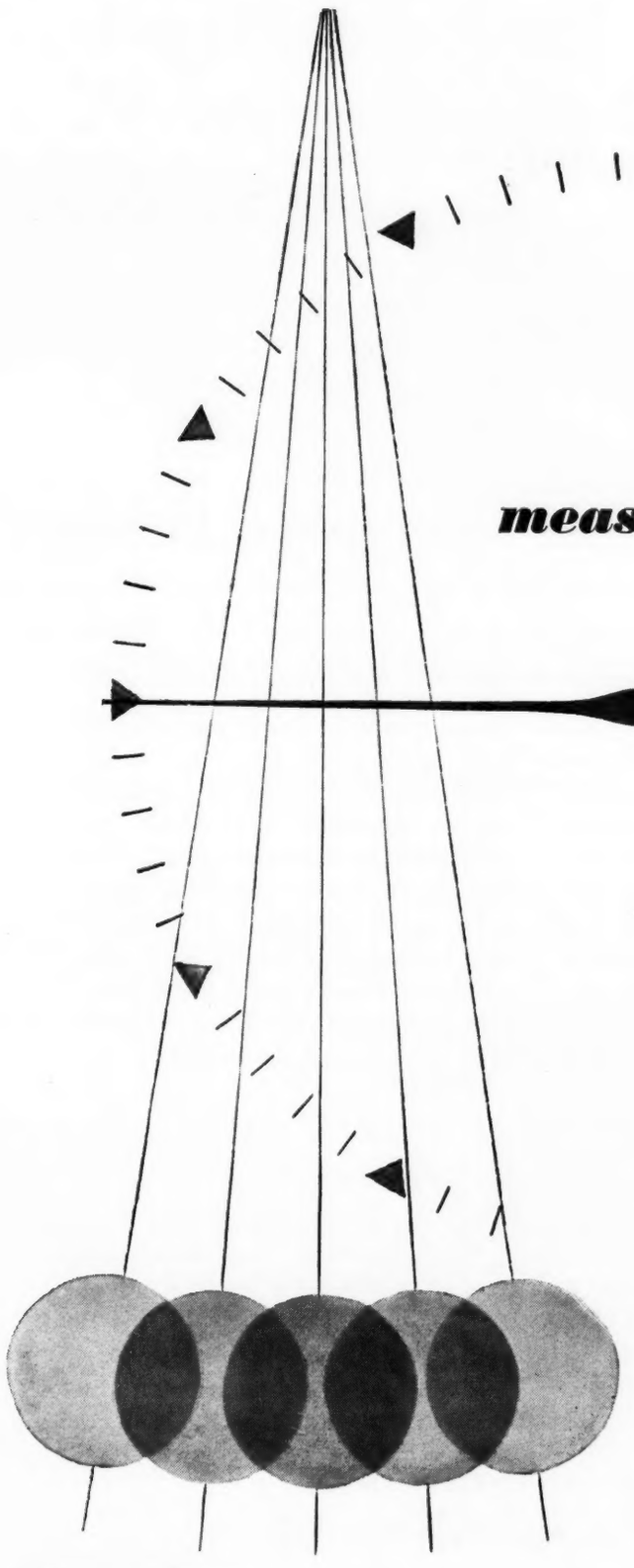
antidote for spasm

Tension of body and mind whether of central or autonomic origin finds a safe, pleasant antidote in Barbidonna. This logical combination of the natural belladonna alkaloids and phenobarbital affords the smooth spasmolysis . . . the balanced sedation . . . so essential for rapid control of smooth muscle spasm in the gastro-intestinal, cardiovascular, respiratory or urogenital tracts and psycho-tension of the central nervous system. Write today for further information and a professional sample.

Formula: Each tablet or fluidram (4 cc.) of elixir contains:
Phenobarbital . . . . . 16.0 mg. (¼ gr.)
Belladonna Alkaloids . . . . . 0.134 mg.
(approximately equivalent to ½ gr. belladonna leaves or 7 min. Tr. belladonna)
Tablets: in bottles of 100, 500 and 1000
Elixir: in bottles of 1 pint and 1 gallon

BARBIDONNA

VANPELT & BROWN, INC. *Pharmaceutical Chemists* **RICHMOND, VIRGINIA**



measured in minutes

Rapid anticoagulant effects are available with Heparin Sodium preparations, developed by Upjohn research workers. In a matter of minutes, coagulation time can be lengthened to offset danger from thrombosis and embolism. With Depo*-Heparin Sodium, prolonged effects lasting 20 to 24 hours may be obtained with a single injection. Therapy with these Upjohn anticoagulants is distinguished by promptness of action, simplicity of supervision, and ready controllability.

**Trademark, Reg. U. S. Pat. Off.*

Upjohn ***Medicine...Produced with care...Designed for health***

THE UPJOHN COMPANY, KALAMAZOO 99, MICHIGAN

Resistant

wounds, burns,
ulcerations,
dermatoses

often **respond**

to Chloresium chlorophyll therapy!

In chronic conditions, the *problem* is how to provide a local condition conducive to normal tissue repair. Clinical reports on large series of such cases show that the *answer* is often Chloresium. And these water-soluble chlorophyll preparations provide the added advantages of deodorizing and cleaning up foul-smelling wounds and ulcerations, relieving itching and local irritation.

From some 30 published reports covering more than 1150 cases, the following excerpt perhaps best summarizes Chloresium's positive action:*

"These patients (compound fracture cases with osteomyelitis and widely open wounds in a military hospital) were so malodorous as to deprive patients and attendants of appetite. Our first observation on beginning use of chlorophyll (Chloresium) was that this odor immediately disappeared, and next we observed a great improvement in appearance of the wounds . . ."

*Bowers, W. F., *Am. J. of Surg.*, LXXIII; 37 (1947)

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Advantages of Chloresium

1. **Promotes the growth of healthy granulation tissue.**
2. **Helps produce a clean, granulating wound base.**
3. **Provides relief from itching and local irritation.**
4. **Helps in burns and dermatoses to bring about normal repair and epithelization.**
5. **Deodorizes malodorous lesions.**
6. **Is nontoxic, bland and soothing.**

RYSTAN COMPANY, INC.
7 N. MacQuesten Pkwy., Mt. Vernon, N. Y.

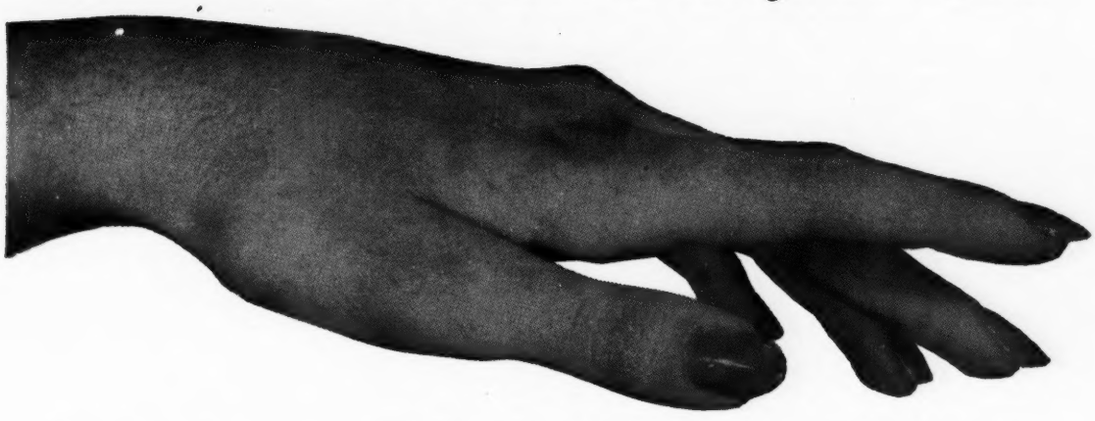
Literature and samples on request

Chloresium
REG. U.S. PAT. OFF.

Ointment—1-oz. and 4-oz. tubes
Solution (Plain)—2-oz. and 8-oz. bottles

From Youth to Age

Benzestrol Covers Your Estrogenic Problems

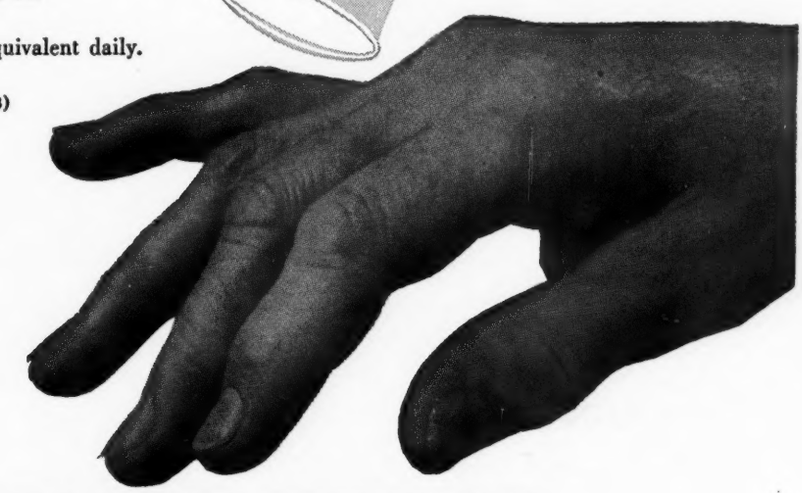


"Benzestrol, in my experience, provides prolonged beneficial effects . . . . Undesirable side reactions, . . . were not encountered in my experience . . . In general also there seemed to be quite a decided improvement in the vague arthropathies and hypertensions associated with the menopausal syndromes."*

The Effective, Non-toxic, Synthetic Estrogen
Available in all Dosage Forms:

Oral Tablets: 0.5 mg., 1.0 mg., 2.0 mg., 5.0 mg.
Vaginal Tablets: 0.5 mg.
Injectable Solution: 5.0 mg. per cc.
Elixir: 2.0 mg. per teaspoonful.
Average Dose: 1 to 2 mg. or equivalent daily.

*Hufford, A.R.: J.A.M.A., *123*, 259, (1943)



ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Schieffelin **BENZESTROL**

2, 4 - di (p - hydroxyphenyl) - 3 - ethyl hexane
Clinical abstracts, literature and samples on request.

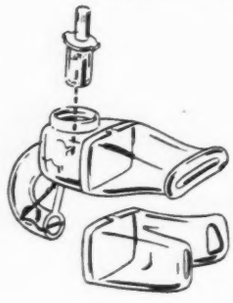
Schieffelin QUALITY INTEGRITY SERVICE

Schieffelin & Co.
24 Cooper Square, New York 3, N. Y.

Have you tried the *Aerohalor* in treating

Tracheitis and Laryngitis?

There is evidence that warrants the use of penicillin powder inhalation with the AEROHALOR in treating tracheitis and laryngitis. • Comparing throat, nose and sputum cultures of a group of patients prior to and following penicillin powder inhalation therapy, Krasno, Karp and Rhoads[1] report "a decided reduction in the number of, or complete disappearance of, gram-positive bacteria." And "in many instances there was a decided decrease in the number of gram-negative bacteria that could be cultured from the same areas following the inhalation of penicillin dust." Frequently these results were accomplished following one inhalation treatment (100,000 units). • The authors state that "on occasion the pain of an acutely sore throat was ameliorated in one-half to one hour following a treatment. These phenomena cannot be fully explained on the basis of the known properties of penicillin and need further investigation." They also report "with assurance" that bacterial infections of the larynx and trachea of fairly recent origin "respond well" to penicillin powder inhalation. • In another reference, Krasno and Rhoads[2] "have successfully treated a number of patients with laryngitis in which the infection was an extension of a nasopharyngitis. Throat cultures taken at various intervals in obstinate cases may help to identify the etiologic basis of this condition." • Effective penicillin powder inhalation therapy is reduced to its simplest terms with the AEROHALOR. The patient simply smokes it like a pipe. No extraneous tubes, valves or oxygen tanks required. For comprehensive literature take a moment now and write to Abbott Laboratories, North Chicago, Illinois. Abbott



AEROHALOR comes assembled with detachable mouthpiece. Easily interchangeable nosepiece included in package. Disposable AEROHALOR* Cartridge containing 100,000 units of finely powdered penicillin G potassium is prescribed separately—3 to a vial.

*Trade Mark for Abbott Sifter Cartridge. AEROHALOR and AEROHALOR Cartridge patented in U. S. and foreign countries.

Aerohalor®

(ABBOTT'S POWDER INHALER)

1. Krasno, L., Karp, M., and Rhoads, P. (1948), The Inhalation of Penicillin Dust, J. Amer. Med. Assn., 138:344, October 2.

2. Krasno, L., and Rhoads, P. (1949), The Inhalation of Penicillin Dust; Its Proper Role in the Management of Respiratory Infections, Amer. Prac., 11:649, July.

AT THE FIRST SNEEZE

That's the sign for SYNTHENATE TARTRATE therapy ... for, in the early phase of coryza, this simple treatment brings gratifying, often dramatic relief.

In 65% of cases complete remission of symptoms occurs within fifteen minutes after injection of 1 cc of SYNTHENATE TARTRATE-Breon, when administered within twenty-four hours of the first sign of a cold!

Injection is simple...relatively nontoxic...prolonged in effect. SYNTHENATE TARTRATE-Breon increases cardiac efficiency and frequently slows the pulse rate; thus it is effective without appreciably increasing the work of the heart. It does not cause cardiac arrhythmias, does not stimulate the central nervous system, does not produce signs of anxiety.

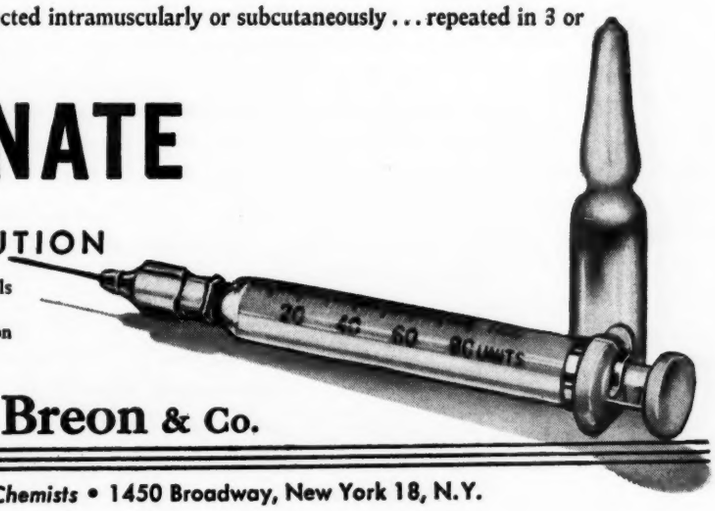
DOSAGE: 1 cc injected intramuscularly or subcutaneously ... repeated in 3 or 4 hours, if required.

SYNTHENATE

Trademark

TARTRATE SOLUTION

Available at all drug stores. 1 cc ampuls — boxes of 12 and 25.
Complete literature to physicians on request.

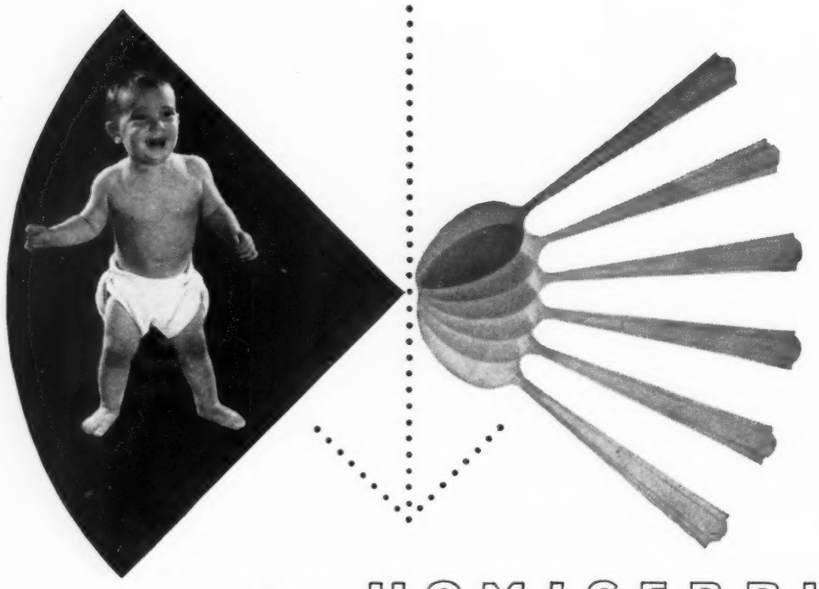


BREON

George A. Breon & Co.

Pharmaceutical Chemists • 1450 Broadway, New York 18, N.Y.

how to get the most out of vitamins



The natural oil globules in **HOMICEBRIN**

(Homogenized Vitamins A, B_1, B_2, C, and D, Lilly), as in milk, are so finely subdivided that they are easily and completely assimilated. Such minute particles readily surrender their vitamin content to the delicate digestive tract of even the smallest infant. The essential water-soluble factors further round out this formula to give young patients full protection from vitamin deficiencies.

The new pint-size economy package reduces the cost of the daily dose in early infancy to less than two cents.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

Complete literature on Lilly vitamin products for prescription use is available from your Lilly medical service representative or will be forwarded upon request.

The American Journal of Medicine

VOL. X MARCH, 1951 No. 3

Editorial

Psyche, Soma and the Steroids

In the drama of modern medicine cortisone and ACTH are playing, for the moment at least, the leading roles. The demonstration of the sudden relief of pain in patients with rheumatoid arthritis is thrilling indeed. Similar astounding effects have been noted in a variety of diseases. The physiologic alterations have been shown to be profound. One of the most fascinating clinical aspects is the effect on behavior. There is a tendency to ascribe the change in personality to the sudden disappearance of pain. However, the more carefully patients are studied the more clear does it become that other factors are involved.

Rome and Braceland[1] describe the effect very well. "The realization of relief (from pain) is accompanied by a feeling of well being, a burgeoning sense of self-confidence, an optimistic, elated mood and an acceleration in the tempo of thinking and physical activity. In every respect this appears to be an appropriate and proportionate response of relatively brief duration, to the relief of the physical and conscious psychologic stress of symptoms." However, these workers observed that the biologic variation in the effect of the hormones on the psyche seemed to be fully as great as the variation in physiologic response or the clinical manifestations. Some patients expressed the change in such statements as: "I'm on top of the world and it is hard to sit still when you feel as good as this." The reaction is interpreted by Rome and Braceland as a "direct consequence of a rejuvenated hope and the conscious appreciation of a relief from invalidism." Other patients "were obviously stimulated, and their thinking and behavior was accelerated to the point of mental excitement, restlessness and a rapidly fluctuant mood. During periods of elation they tended to be facetious or even silly." Another group was "characterized by pronounced anxiety, physical tension and hyperkinesis, phobic and other ruminative preoccupations and a narcissistic overevaluation of their physical person. . . . Within a variable time after the administration of ACTH or cortisone was begun, their particular personality conflicts were fulminated. Those whose psychodynamic organizations were cyclothymic experienced mild hypomania or mild depression or both. Similarly, those patients who could be characterized as obsessional developed phobias and ritualistic behavior with consistent response of affect." Clinically overt psychosis was relatively unusual and of brief duration. Its character was determined entirely by the patient's prepsychotic personality. These preliminary observations "led to the assumption that the sudden and profound variation in the milieu interior which so markedly effects the patient's metabolic homeostasis is similarly disruptive of his psychologic adaptation."

Boland and Headley[2] also mention the psychic changes: euphoria, insomnia, restlessness and "nervous tension." "Increased mental activity and capacity and a clearing up of thought processes were described by

[1] ROME, HOWARD P. and BRACELAND, FRANCIS J. Use of cortisone and ACTH in certain diseases: psychiatric aspects. *Proc. Staff Meet., Mayo Clin.*, 25: 495–497 1950.

[2] BOLAND, EDWARD W. and HEADLEY, NATHAN E. Management of rheumatoid arthritis with smaller (maintenance) doses of cortisone acetate. *J. A. M. A.*, 144: 365–372, 1950.

several (patients). Some patients found themselves with new ideas or business schemes, and their increased psychomotor function and drive was expressed through purposeful and gainful activity."

Mote[3] concludes that "most patients receiving ACTH are inclined to develop a sense of well being and a sense of mental activity bordering on euphoria, regardless of the disease in question. Electroencephalographic recordings . . . reveal that the alpha waves are of both larger magnitude and shorter intervals. . . . Patients on high doses of ACTH should be watched carefully from a psychiatric viewpoint since over-stimulation may bring subclinical psychoses to the clinical level." These observations suggest that the alteration in the psyche does not result merely from the relief of physical pain or improvement in the disease process.

An interesting experience[4] has been gained with patients afflicted with chronic ulcerative colitis, a disease frequently accompanied by profound emotional disturbances. The usual ACTH effect is an improved sense of well being and an increased appetite. Euphoria is not infrequent. In a few patients no change at all is noted. It is difficult to appraise even roughly the mechanisms involved. Cessation of the diarrhea in ulcerative colitis usually leads to an improved appetite, sense of well being and even euphoria, regardless of the therapy employed. Nevertheless, the impression has been gained that the effect of ACTH upon certain individuals is not to be explained so simply. The patient's mood may change in a few hours before there is any observable alteration in the function of the bowel. Furthermore, the elation and euphoria may persist in spite of rather severe recurrences of the diarrhea. In one patient a prolonged and severe depression lifted completely for the several weeks during which ACTH was administered even though there were rather transitory recurrences of the diarrhea. On the other hand, when injections of a placebo were substituted for ACTH the depression quickly recurred. This observation was repeated several times. The patient soon learned by means of his sense of well being to tell the difference between the placebo and ACTH. In another patient, when a placebo was substituted for ACTH the euphoria and hyperkinesis disappeared rapidly to be replaced by depression and somnolence with no alteration in the function of the bowel. A third patient receiving physiologically inadequate amounts of hormone, as judged by the eosinophile count, became euphoric within a few hours after the administration of a larger dose. A querulous, whining, depressed and withdrawn young woman completely incapacitated for several years from ulcerative colitis became aggressive and outgoing even though there was little or no influence upon her diarrhea; she regained an interest in life and evinced a willingness to accept an ileostomy as a means of rehabilitation whereas previously she had refused repeatedly even to consider the possibility. On the other hand, in three patients with severe depression brief courses of ACTH yielded little or no improvement. Nevertheless, experiences such as those mentioned suggest a direct hormonal effect upon the personality. Perhaps ACTH and cortisone may offer an entirely new approach to many problems in human behavior. Certainly at times they provide the physician with a potent therapeutic weapon even though it is not possible at present to predict with accuracy the extent or type of effect.

Other steroid hormones may be found to play important psychosomatic roles. The anabolic effects of the estrogens and androgens is well known. The improvement in the sense of well being following their administration is variable but at times definite. The sex differences are fascinating and difficult to understand. Thus estrogens, in addition to relieving the hot flashes of the menopause, not infrequently seem to bring about general improvement. Women with carcinoma of the breast may feel better and gain weight

[3] Mote, John R. Personal communication.

[4] Kirsner, Joseph B. and Palmer, Walter L. To be published.

following the administration of estrogens as well as androgens even though there may be no discernible inhibition of the cancer. Similarly, in men with prostatic neoplasm, estrogens may result in clinical improvement not entirely attributable to the effect on the tumor.

Another curious phenomenon is the effect of the various steroid hormones upon the libido which is, in a sense, one of the most sensitive indicators of both the psyche and the soma. ACTH and cortisone are reported to exert relatively little influence. Under therapy with ACTH both loss of libido with impotence and increased libido with competence have been observed in male patients under control conditions suggesting hormonal rather than psychic mechanisms.[4] There is little or no evidence of any direct or specific effect. Boland and Headley[2] report that four of eighteen men receiving cortisone noted increased libido and potentia; no decreased libido or impotence was recorded; the women patients denied any change in libido. Estrogens in the menopausal female may be stimulative but the effect is certainly not constant and perhaps is debatable. Prepuberal castration in both sexes prevents sexual development; in the adult human female castration usually does not reduce the libido as is evident from the testimony of patients and the failure of the operation to relieve nymphomania; in the adult male castration likewise may not depress libido or produce impotence.[5,6] On the other hand, estrogens administered to elderly men in the treatment of prostatic neoplasm almost invariably destroy any remaining libido and produce impotence. Androgens administered to adult men have little or no effect upon the libido[7,8] whereas in the female they may be profound stimulants even in women well past the menopause. There is no hormone which will produce in the postpuberal, non-castrated male anything remotely resembling the libidinal stimulation noted in some females after the administration of large amounts of androgen. The effect of androgens on the personality is not limited to the sexual sphere. It will be recalled that Allee[9] altered the "peck order" of hens by testosterone; the hens became more aggressive. Similarly the aggressiveness of prepuberal male castrates may be markedly increased by the administration of androgens.

Doubtless decades of work will be required to solve the many problems of the adrenal cortex and the steroid hormones. It is clear that health, disease and behavior are not simply matters of the body or of the mind; innumerable factors are involved. It is safe to predict that many hormonal links will be found between the psyche and the soma. Elucidation of the role of the steroids in disease, in health and in alteration of personality presents a thrilling challenge to investigators in many fields.

WALTER L. PALMER, M.D.

[5] BEACH, FRANK A. Hormones and Behavior. New York, 1948. Paul B. Hoeber, Inc.

[6] BEACH, FRANK A. Sexual behavior in animals and men. *Harvey Lect.*, Series 43, pp. 255–280, 1947–1948.

[7] CARMICHAEL, HUGH T., NOONAN, WILLIAM J. and KENYON, ALLAN T. The effects of testosterone propionate in impotence. *Am. J. Psychiat.*, 97: 19–941, 1941.

[8] KENYON, ALLAN T. Problems in the recognition and treatment of testicular insufficiency. *New England J. Med.*, 225: 714–719, 1941.

[9] ALLEE, W. C., COLLIAS, N. E. and LUTHERMAN, CATHARINE Z. Modification of the social order in flocks of hens by the injection of testosterone propionate. *Physiol. Zoöl.*, 12: 412–440, 1939.

Clinical Studies

Treatment of Enterococcal Endocarditis and Bacteremia*

Results of Combined Therapy with Penicillin and Streptomycin

WILLIAM C. ROBBINS, M.D.† *and* RALPH TOMPSETT, M.D.
New York, New York

THE effectiveness of penicillin therapy in most cases of subacute streptococcal endocarditis has focused attention on a small but important group of patients in whom the infecting organisms are highly resistant to penicillin. Arrest of the infection in these cases, which comprise 5 to 10 per cent of all cases of subacute bacterial endocarditis, has been difficult if not impossible to achieve. In contrast to the more commonly encountered cases of subacute bacterial endocarditis which are caused by members of the Streptococcus viridans group, the highly penicillin-resistant streptococci have generally been found to belong to the enterococcus subdivision of the genus Streptococcus. The two most important species of this subdivision from the standpoint of human disease are Streptococcus fecalis and Streptococcus zymogenes.

The biologic characteristics of the enterococci and their association with human infections have been extensively reviewed by others.[1–6] Briefly, it may be said that these organisms are streptococci which are present in the normal intestinal flora and in milk and milk products. They usually do not form long chains but occur as diplococci or in short chains. They are insoluble in bile, hydrolyze mannite, and are markedly resistant to wide variations in environmental heat, pH and salt concentration, as well as to the presence of antimicrobial substances. Extracts of these organisms form precipitate with Lancefield Group D antiserum. On blood agar the colonies may be non-hemolytic or they may exhibit alpha or beta hemolysis. Consequently, when a strain is isolated by blood culture it may erroneously be assumed to be an unclassified non-hemolytic streptococcus, a Streptococcus viridans or a Group A hemolytic streptococcus. The true nature of the strain, therefore, may be unrecognized unless further laboratory tests are performed. In practice, the identity of such organisms is frequently first suspected from the results of the *in vitro* penicillin sensitivity tests, or because of the failure of the patient to respond to the usual doses of penicillin. The concentration of penicillin required to inhibit growth of enterococci *in vitro* is almost without exception greater than 1.0 unit per cc. of medium, and for the majority of strains the minimal inhibitory concentration is from 3.0 to 6.0 units per cc.[7,8] This degree of resistance is in striking contrast to the sensitivity range displayed by members of the Streptococcus viridans group (from 0.02 to 0.3 unit of penicillin per cc.)

* From the Department of Medicine, New York Hospital-Cornell Medical Center, New York, N.Y. Presented in part at the Second National Symposium on Antibiotics of the National Institutes of Health, Washington, D.C., April 11–12, 1949. This study was aided in part by grants from: The Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service; the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York; and Charles Pfizer and Company, Brooklyn, New York.

† National Institutes of Health Post-doctorate Fellow in Medicine.

and by Group A hemolytic streptococci (inhibited by 0.02 unit of penicillin per cc. or less).

The clinical features of enterococcal endocarditis have been thoroughly described.[4–6] In general, the symptomatology and physical findings are similar to those seen in Streptococcus viridans endocarditis. There are certain features which are different, however. Because enterococci are commonly present in the gastrointestinal tract and are not infrequent invaders of the urinary tract and female genital tract, males are most apt to become infected during or following surgical operations on the genitourinary system, notably the prostate, and infections in females are frequently related to abortions or pregnancy. Consequently, the age groups affected are quite different for the two sexes. Most male patients are over forty-five years of age while most female patients are of the childbearing age, from twenty to forty. Recently, several cases of postoperative enterococcal endocarditis following surgical procedures on the heart and great vessels for correction of congenital abnormalities have been reported.[26] The mode of infection in these cases is not clear but the possibility exists that multiple invasion of the blood stream occurred at operation or postoperatively and that routine postoperative antimicrobial therapy eliminated all but the most resistant parasites. No such infections caused by Streptococcus viridans have been reported.

In addition to the above features, enterococcal endocarditis differs clinically from Streptococcus viridans endocarditis in its propensity for gross abscess formation, most often in the spleen, during the course of the disease.[4,6]

The treatment of enterococcal endocarditis has posed a difficult problem. It has been apparent from the outset that the doses of penicillin which are usually employed in the treatment of subacute bacterial endocarditis, of the order of one million units daily, are ineffective. Larger doses may result in temporary improvement and sometimes reverse bacteremia but prompt relapse has almost invariably ensued upon cessation of treatment.[6,12] In occasional cases arrest of the infection has been achieved by prolonged therapy with massive doses of penicillin, i.e., total daily doses of 12 to 60 million units over long periods of time.[9,11] In some of these successful cases the concurrent use of carinamide, or the presence of impaired renal function, aided in maintaining a sufficiently high concentration of penicillin in the body to contribute materially to the control of the infection.

The exact value of streptomycin in the treatment of enterococcal endocarditis has not been established. Strains isolated from patients prior to streptomycin administration exhibit moderate to high degrees of resistance to streptomycin *in vitro*. Inhibitory concentrations range from 3 to 100 micrograms per cc., usually between 4 and 22 micrograms per cc.[8] There has been considerable pessimism concerning the value of streptomycin in bacterial endocarditis for two reasons: First, the administration of streptomycin for the prolonged periods necessary in this disease is accompanied by certain hazards due to toxicity of the drug. Second, there is always present the danger of emergence of drug-resistant strains of bacteria. These limitations, particularly the latter, may well have restricted the use of streptomycin as a single agent in this disease.

The few cases reported treated with streptomycin alone indicate that failure is more the rule than is success. Hunter[12] met with failure in two patients treated with streptomycin. In one the organism isolated while the patient was on streptomycin was found to have increased sharply in resistance to the drug *in vitro*. Results in the group of five cases assembled by Keefer and Hewitt,[13] most of which received brief courses of streptomycin, however, are equally poor. One of the five, a failure, is reported in detail by Cady.[14] Boger et al.[15] treated a patient with streptococcal endocarditis unsuccessfully with streptomycin, the organism increasing in *in vitro* resistance 2,000 times

in the space of ten days of streptomycin administration. Cressy et al.[16] met with failure in the streptomycin treatment of a patient with endocarditis caused by a penicillin-resistant streptococcus, probably an enterococcus. In this case also, the emergence of very resistant members of the infecting population was demonstrated within two weeks of the commencement of streptomycin therapy. Adcock[17] recently observed a patient with enterococcal endocarditis who had received prior streptomycin therapy and whose infecting organism grew in 500 but not in 1,000 micrograms of streptomycin per cc. *in vitro*. Stuart-Harris et al.[11] reported two cases of chronically relapsing penicillin-resistant streptococcal endocarditis treated with long courses of streptomycin. In both cases failure resulted and was accompanied by the emergence of a more streptomycin-resistant strain. However, Naegele[18] reported the successful employment of streptomycin in two patients infected with highly penicillin-resistant streptococci (possibly enterococci), and Zeller et al.[19] effected the arrest of one patient's infection by the use of a long course of streptomycin pursuant to a suppressive but not eradicative course of penicillin. Guss[20] reported a favorable result in one patient following streptomycin treatment, although it is not clear from the report whether the patient received concurrent penicillin or not.

It is apparent from the above limited experience that, in general, streptomycin administration has met with little success in the treatment of enterococcal or of penicillin-resistant streptococcal endocarditis; and in some cases the subsequent emergence of streptomycin-fast organisms has occurred. It may be fairly stated that recoveries following the use of the one drug alone have been only sporadic.

Hunter,[12] in 1947, first reported the successful use of concurrent penicillin and streptomycin in the treatment of a patient with enterococcal endocarditis.* Since that time, seven patients with enterococcal endocarditis have been treated at the New York Hospital Cornell Medical Center and on the Second Medical Division (Cornell) of Bellevue Hospital* with a regimen of concurrent penicillin and streptomycin. The purpose of this paper is to report these cases with the results of treatment. The cases are unselected and represent all of the patients with enterococcal endocarditis admitted to these two services since January, 1947. The organisms isolated from these patients all possessed the biologic characteristics of the enterococci and all gave a positive reaction with Lancefield Group D antiserum. In addition, there is included one case of subacute bacterial endocarditis due to a nonhemolytic streptococcus which was highly resistant to penicillin and which possessed many of the biologic characteristics of the enterococci but which failed to ferment mannite or to react with Lancefield Group D antiserum (Case VIII). This case represented a closely similar but not identical therapeutic problem to the other seven, all of which were caused by Lancefield Group D streptococci (enterococci).

The results encountered with the combined treatment of this group of patients are considered encouraging. The regimen employed was the concurrent administration of 500,000 units of crystalline penicillin intramuscularly every two hours and of 0.5 gm. of streptomycin or dihydrostreptomycin intramuscularly four times daily. The patients thus received a total dosage of 6 million units of penicillin and 2 gm. of streptomycin each day. Whenever possible, this regimen was continued for a period of twenty-eight to forty-two days.

CASE REPORTS AND CLINICAL OBSERVATIONS

CASE I. *Enterococcal endocarditis; heart disease of undetermined type.* (Fig. 1.) H. B., a sixty year old white male drawbridge operator, was admitted to the New York Hospital on April 12, 1947. The patient had developed a urethral stricture following gonorrhea thirty-five years previously

* This case is the one recovery of the five cases collected by Keefer and Hewitt.[13]

* One of the seven patients was treated at Grasslands Hospital, Valhalla, N. Y.

and during the ensuing years he had been treated frequently by the passage of sounds. Two days before the onset of his present illness sounds had been passed again. On December 5, 1946, he experienced a chill and feverishness, followed by the development of malaise, easy fatigability, anorexia, weight loss and night sweats. He received a brief course of sulfonamide and penicillin therapy with some clinical improvement. The illness continued, however, and three months prior to admission he experienced severe low back pain with sciatic radiation. Two months prior to admission there appeared in succession painful erythematous areas on the right forearm, right thumb and left little finger. He entered another hospital in March, 1947, where two blood cultures were positive for an enterococcus and Alkaligenes faecalis was grown from the urine. A ten-day course of penicillin therapy followed by seven days of streptomycin was without appreciable effect on the illness and he was discharged unimproved.

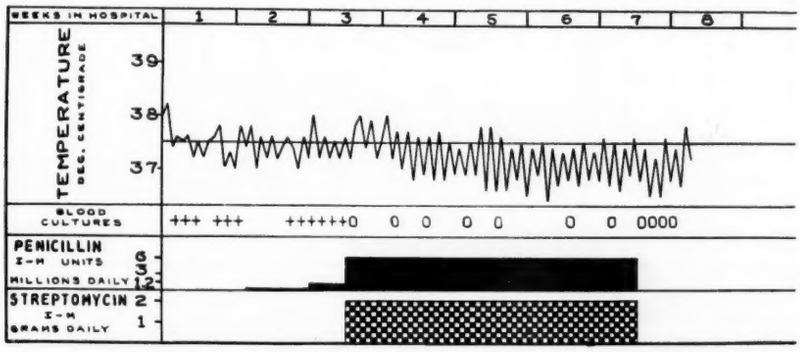


FIG. 1. Case 1. H. B., a white male age sixty, with enterococcal endocarditis and heart disease of undetermined type. The administration of 2 gm. of streptomycin daily concurrently with 6 million units of penicillin daily resulted in arrest of the infection.

On admission to the New York Hospital the patient was an elderly man who presented evidence of chronic illness and weight loss. The temperature was 37.6°C., pulse rate 86, respiratory rate 20 and blood pressure 150/70 mm. Hg. The teeth were carious. The heart was not enlarged to examination and was in normal sinus rhythm. There was a soft, non-transmitted systolic murmur at the apex. The tip of the spleen was felt under the costal margin. There was slight clubbing of the fingers. The urine contained a trace of albumin, 6 to 10 leukocytes, and an occasional erythrocyte per high power field. Cultures of the urine from the bladder and both ureters were sterile. Roentgenographic examination of the chest revealed mild emphysema but was otherwise negative. An electrocardiogram was remarkable only for low QRS complexes in leads 1, 2 and 3 and a deep, inverted QRS 4, possibly indicating myocardial damage. A complete investigation of the urinary tract including retrograde pyelography revealed only bladder diverticula and a urethral stricture.

Blood cultures taken daily from the day of admission were positive for a non-hemolytic streptococcus. This organism was an enterococcus (Lancefield Group D streptococcus) inhibited *in vitro* by 6 but not by 5 units of penicillin per cc. and inhibited by 8 but not by 5.5 micrograms of streptomycin per cc.

On April 21, 1947, penicillin therapy was begun, the patient receiving a daily total of 400,000 units by intramuscular injection. When the resistance of the organism to penicillin became known, penicillin was increased to 1.2 million units daily, but blood cultures continued to be positive. On April 30th combined therapy* was started. The patient received 6 million units of penicillin (500,000 units every two hours intramuscularly) daily for twenty-eight days. Bacteremia was reversed within twenty-four hours and remained so thenceforth. The patient improved steadily during therapy, his temperature becoming normal during the second week and remaining so. During his hospital stay the apical systolic murmur present on admission became more harsh and easily heard over the precordium and in the axilla. He was discharged to the follow-up clinic on June 5, 1947.

* The term *combined therapy* refers to the concurrent administration of two or more chemotherapeutic agents to the same patient.

The patient has been seen at frequent intervals since discharge. He has remained free of any recurrence for twenty-one months and has returned to work. His infection is considered to be arrested.

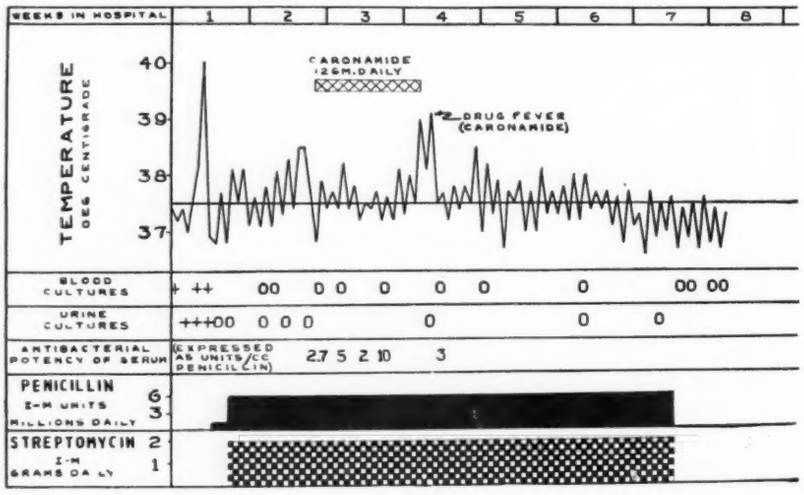


FIG. 2. Case II. I. T., a white male age fifty-seven, with subacute enterococcal bacteremia and probable endocarditis. Combined penicillin and streptomycin therapy resulted in prompt arrest of the infection.

Comment. The course of events in this case illustrates several features of enterococcal bacteremia and infection of the heart valves. The onset of infection in males is often closely related to instrumentation of the urethra and infection of the urinary tract. Treatment with penicillin in doses of 100,000 units every two hours was insufficient to reverse the bacteremia. (Fig. 1.) Combined penicillin and streptomycin therapy resulted in a prompt defervescence and in arrest of the infection.

CASE II. *Subacute enterococcal bacteremia and probable endocarditis.* (Fig. 2.) I. T., a fifty-seven year old white male inspector, was admitted to the New York Hospital on March 14, 1948. Eight weeks prior to admission the patient was cystoscoped because of hematuria and was told that a bladder tumor was found. Three days following this procedure he developed chills and fever and was admitted to another hospital where he received low-dosage penicillin therapy for several days. Following discharge he experienced increasingly severe afternoon fever, night sweats, anorexia, weight loss and chills. Two weeks before admission to this hospital he developed tender erythematous swellings of the right heel and left elbow. There was no history of rheumatic fever.

On admission to the New York Hospital the patient appeared chronically ill. The temperature was 37.4°C., pulse rate 80, respiratory rate 20 and blood pressure 125/75 mm. Hg. The lungs were clear except for an occasional coarse rhonchus. The heart was not enlarged to examination and was in normal sinus rhythm. Because of marked emphysema the heart sounds were faint and distant, although of good quality. The first sound at the apex was accentuated but no murmurs nor thrills were detected. The liver edge was soft and non-tender and extended 3 cm. below the costal margin. The spleen was enlarged 1 cm. below the costal margin. There was no costovertebral angle tenderness, but there was spasm of the muscles of the lumbar region, and straight leg-raising elicited severe discomfort in this region. There was extreme tenderness on digital pressure high in the rectum. The hemoglobin concentration was 14.2 gm. per cent and there were 4.9 million erythrocytes per cu. mm. and 5.3 thousand leukocytes per cu. mm. The urine contained a rare erythrocyte and an occasional leukocyte. A urine culture was positive for Streptococcus zymogenes (hemolytic enterococcus). The electrocardiographic findings were suggestive of early right axis deviation but otherwise were normal. Intravenous pyelography revealed no abnormalities of the urinary tract.

Three blood cultures taken during the first four days of hospitalization were positive for a

beta-hemolytic Lancefield Group D streptococcus (*Streptococcus zymogenes*), 175 to 200 colonies per cc. This enterococcus was inhibited *in vitro* by 6 but not by 5 units of penicillin per cc., and inhibited by 22 but not by 16 micrograms of streptomycin per cc..

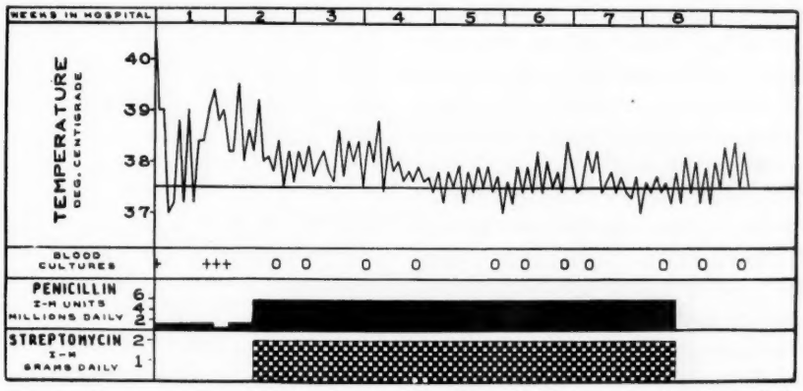


FIG. 3. Case III. S. I., a white male age forty-five with enterococcal endocarditis and chronic rheumatic valvulitis. Although in cardiac failure, the patient made a striking recovery as the result of combined penicillin and streptomycin therapy of six weeks' duration.

The patient was started on 1.2 million units of penicillin daily on the third hospital day; combined therapy was begun on the fifth hospital day. He received 6 million units of penicillin and 2 gm. of streptomycin daily without interruption for the ensuing forty-five days. Blood cultures and urine cultures were sterile from the beginning of the combined regimen and remained so. On the fourteenth hospital day the patient was given carinamide, 2 gm. every four hours, but developed a febrile reaction so that it was discontinued after eight days. There was steady improvement following the commencement of combined therapy, the fever and back pain subsiding slowly. On discharge, May 4, 1948, the spleen was no longer palpable.

The patient was seen one month and one year after discharge at which times blood cultures were negative and there was no evidence of recurrence. The infection is considered to be arrested.

Comment. This patient's infection apparently stemmed from the urinary tract instrumentation performed two months prior to his admission to this hospital. Although no cardiac murmur was detected, the likelihood that infection was present in the heart valves is considered strong. The organism was a hemolytic enterococcus highly resistant to penicillin and moderately resistant to streptomycin. The response to six weeks of combined therapy with the two drugs was striking and the remission has been lasting. Carinamide, administered in low dosage for only eight days, did not appear to play any role in the arrest of this patient's disease.

CASE III. *Enterococcal endocarditis and chronic rheumatic valvulitis.* (Fig. 3.) S. I., a forty-five year old white male office clerk, was admitted to the New York Hospital on July 28, 1948. At the age of fifteen the patient had experienced a typical attack of acute rheumatic fever. At the age of thirty-five he had consulted a physician who prescribed digitalis which the patient took until the time of admission. During the month prior to admission he had experienced anorexia, malaise, nausea and easy fatigability. Three weeks before admission he noted the sudden onset of left upper quadrant pain accentuated by respiration. This pain subsided gradually, but three days prior to admission he began to have chills and fever, developed pain in the left chest and a cough productive of blood-tinged sputum.

On admission the patient was acutely ill, with labored respirations and cyanosis. His temperature was 40.4°C., the heart rate was 180, radial pulse 76, respiratory rate 32 and blood pressure 98/68 mm. Hg. The skin was pale, slightly icteric and cyanotic. There were signs of fluid at the right lung base and coarse inspiratory rales were present at both lung bases. The heart was markedly enlarged to the left and right and was in grossly irregular rhythm. A harsh systolic

murmur and a low rumbling diastolic murmur with presystolic crescendo and a slapping first sound were heard at the apex. A systolic thrill was present at the apex. The liver was felt at the costal margin and was slightly tender. The spleen was not enlarged and there was no edema. There was a mild hypochromic anemia and the total leukocyte count was 27.2 thousand per cu. mm. The urine contained a trace of albumin and 10 to 12 leukocytes per high power field. The serum bilirubin was 8.1 mg. per 100 cc. A chest roentgenogram revealed mottled densities widely spread throughout both lung fields, bilateral pleural effusion and generalized cardiac enlargement. An electrocardiogram showed auricular fibrillation, ventricular premature contractions, and a low QRS 1. Nonhemolytic streptococci and E. coli were isolated from the sputum culture.

Blood culture drawn on the day of admission and five blood cultures taken on the sixth, seventh and eighth hospital days were all positive for a non-hemolytic streptococcus. This organism was an enterococcus which proved to be inhibited *in vitro* by 4 but not by 3 units of penicillin per cc., or by 16 but not by 11 micrograms of streptomycin per cc.

On the night of admission the patient was started on intramuscular penicillin, receiving a daily total of 900,000 units. Therapy with oxygen, digitalis, mercurials and salt restriction was also instituted and there was considerable clinical response. On August 7th a prolonged period of combined therapy was started. A daily total of 6 million units of penicillin and 2 gm. of streptomycin was administered intramuscularly for forty-two days. Two days after beginning the combined regimen the blood culture was sterile and all cultures taken subsequently have been sterile. There was steady clinical improvement during this period and the patient was discharged to the care of his private physician on October 2nd.

Since discharge the patient has been followed for six months, and although he continues to require management for cardiac failure, has been free from any signs of recurrence and blood cultures have remained sterile. The infection is considered to be arrested.

Comment. This patient's infection was decisively controlled by combined penicillin and streptomycin therapy begun early in the course of the disease in spite of the presence of heart failure of considerable degree. The results in this case are in sharp contrast to those obtained in Case VI in which heart failure also was a serious complication and in which increasingly large amounts of penicillin were administered without control of the infection. It is conceivable that the early institution of effective antimicrobial therapy in this case was responsible for the favorable outcome despite the poor prognosis.

CASE IV.* *Enterococcal endocarditis and chronic rheumatic valvulitis.* M. T., a thirty-five year old white housewife, was admitted to Grasslands Hospital, Valhalla, N.Y., on April 12, 1949. The patient had had rheumatic fever at the age of seven but there had been no subsequent disability and she had carried three pregnancies to completion without complication. In January, 1949, a three-month pregnancy was terminated by the use of a non-sterile rubber catheter. One week following this the patient developed fever, chilly sensations and easy fatigability. She was treated with sulfadiazine without improvement and because of the onset of frank chills was admitted to another hospital where blood cultures revealed the presence of enterococcal bacteremia. Penicillin, 900,000 units a day, was administered without appreciable improvement and she was transferred to Grasslands Hospital.

On admission the patient was a well developed, well nourished female who appeared moderately ill. The temperature was 101°F., pulse rate 110 and blood pressure 110/60 mm. Hg. The heart was not enlarged but there was a harsh systolic murmur over the mitral area. The tip of the spleen was palpable at the left costal margin. There was a copious, thin purulent discharge from the cervix. The hemoglobin concentration was 11 gm. per cent; there were 3.6 million erythrocytes per cu. mm. and 13,900 leukocytes per cu. mm. A culture of the cervical discharge revealed enterococci, E. coli and Staphylococcus albus.

Four successive blood cultures were positive for an enterococcus inhibited *in vitro* by 5 but not by 2.5 units of penicillin per cc., or by 8 but not by 3 micrograms of streptomycin per cc.

On April 18, 1949, the patient was started on combined therapy, receiving 500,000 units of

* Included through the courtesy of Dr. Herman Tarnower, Scarsdale, N.Y.

penicillin every two hours and 0.5 gm. of dihydrostreptomycin every six hours for a period of forty days. A blood culture taken twenty-four hours after beginning therapy was sterile and all subsequent cultures were sterile. Transient rises in temperature and two emboli to the femoral arteries, which necessitated paravertebral sympathetic block, were the only significant occurrences during therapy. Otherwise clinical improvement was steady.

The patient has been seen at regular intervals since discharge from the hospital and has remained well. Repeated blood cultures have been sterile and there have been no signs of recurrence of the infection. There is a very slight disability of the right leg as the result of the emboli.

Comment. The course of the illness and response to combined therapy in this case are typical. The prognosis was good because of the good nutritional state and the absence of heart failure. Reversion of bacteremia was prompt and clinical improvement was steady following the institution of concurrent penicillin and streptomycin therapy. The fact that effective antimicrobial therapy gives no assurance against the occurrence of emboli is also illustrated by this case.

CASE V. *Enterococcal endocarditis, chronic rheumatic valvulitis and pelvic inflammatory disease.* A. R., a twenty-nine year old Puerto Rican housewife, was admitted to the Second Medical Division (Cornell) Bellevue Hospital, on February 16, 1949. The chief complaint was that of painful joints.

At the age of fourteen the patient contracted gonorrhea which was never effectively treated. A vaginal discharge was present thereafter. In May, 1948, a spontaneous abortion was followed by a curettage. In July, 1948, the patient again aborted and the curettage was repeated. Fever developed postoperatively for which she was treated with penicillin and sulfonamide. Malaise and easy fatigability persisted, and in November, 1948, the patient received treatment for a urinary tract infection because of the onset of left flank pain and fever. An attack of severe sudden pain in the left hip was followed by polyarthralgia, anorexia, weight loss, night sweats, frequent epistaxes and progressive exertional dyspnea, orthopnea and pedal edema. Severe dysmenorrhea was present with all menses following July, 1948. There was no history of rheumatic fever although it was said the patient had always been frail and "anemic."

On admission to Bellevue Hospital the patient was malnourished, appearing acutely and chronically ill. The temperature was 101.4°F., pulse rate 98, respiratory rate 18 and blood pressure 110/42 mm. Hg. The heart presented a mitral configuration but was of normal size and in normal sinus rhythm. There was a harsh systolic murmur and a short rumbling diastolic murmur at the apex. A typical aortic diastolic murmur was present and there were peripheral signs of aortic regurgitation. The spleen could not be felt. There was severe pain on motion of the right hip. Clubbing of the fingers was present. Pelvic examination on March 14th revealed a creamy cervical discharge and tenderness and thickening of the right adnexa.

The blood hemoglobin concentration was 11.0 gm. per 100 cc., and there were 3.6 million erythrocytes and 6,700 leukocytes per cu. mm. The urinalysis was negative. A urine culture was reported positive for Streptococcus zymogenes. An electrocardiogram and roentgenograms of the chest and the right hip revealed no abnormalities.

Repeated blood cultures grew an enterococcus (Streptococcus zymogenes) inhibited *in vitro* by 3 but not by 2.5 units of penicillin per cc., or by 44 but not by 32 micrograms of streptomycin per cc.

On February 19th the patient was started on 200,000 units of penicillin every three hours. Blood cultures taken on February 21st and 22nd again revealed bacteremia. On February 25th combined intramuscular therapy (600,000 units of penicillin every two hours and 0.5 gm. of streptomycin twice daily) was started. On March 7th dihydrostreptomycin was substituted for streptomycin and the dosage increased to 0.5 gm. four times daily. The patient was maintained on this combined regimen for forty-two days. There was a prompt subsidence of fever and all blood cultures drawn subsequently were sterile. An embolus to the left radial artery occurred three days prior to the commencement of combined therapy. Petechiae were noted on February 28th and March 11th. Menses were heavy and painful and there were repeated epistaxes. There was one episode of sharp left anterior chest pain without cough.

The patient's clinical course was generally uphill. Cardiac failure was controlled on bed

rest, fever was only low grade and the patient gained 9 pounds in weight. On April 11, 1949, all antimicrobial therapy was discontinued after a total of forty-two days of concurrent penicillin and dihydrostreptomycin therapy. Five blood cultures during the ensuing three weeks were sterile. On April 22nd a small tender erythematous area appeared on the dorsum of the right foot. This subsided in a few days and the patient left the hospital feeling well.

Six days following discharge the patient visited the out-patient department and had no complaints. Blood culture taken at that time was sterile. Later that day, however, menstrual flow began and was associated with severe right lower abdominal pain radiating to the right thigh, fever and chills. The next day pain and swelling of the left wrist recurred with high fever and a shaking chill. The patient was readmitted to the Second Medical Division of Bellevue Hospital on May 12, 1949. She again appeared acutely ill with a temperature of 102.4°F., pulse rate of 120, respiratory rate of 24 and blood pressure of 120/30/0 mm. Hg. There was again a tender erythematous area over the volar aspect of the left wrist. Examination of the heart was as before except for a change in the character of the aortic diastolic murmur, which now was a musical "sea-gull" sound. There was tenderness to pressure and rebound tenderness in the right lower quadrant, with radiation of pain to the right anterior thigh. There was pain on digital examination of the cul-de-sac. On pelvic examination a moderate amount of mucopurulent cervical discharge was noted; there was marked tenderness in the right adnexal structures and pain on movement of the uterus. The routine laboratory procedures were unrevealing. Urine and cervical cultures both revealed E. coli.

Four blood cultures were drawn and the patient was started again on concurrent penicillin and dihydrostreptomycin therapy on May 13th. All blood cultures drawn before and after commencement of therapy were sterile. There was a steady fall in temperature and diminution of the right lower quadrant pain during the course of the first week. Nevertheless, the patient complained of increasingly severe epigastric and substernal pain and tenderness which required frequent analgesics. She became nauseated and anorexic, and on May 26th suffered a sudden pain in the left knee. Increasing dyspnea and the appearance of pulmonary rales necessitated digitalization and the use of mercurial diuretics. The second course of combined antimicrobial therapy was discontinued on June 18th after five weeks of continuous therapy. However, the patient's cardiac failure became progressively more severe. The venous pressure rose to 180 mm. of blood. Cyanosis, orthopnea, cough, repeated hemoptysis, and pedal and sacral edema became more prominent and the patient expired on July 21, 1949. Permission for autopsy was not obtained.

Comment. The prognosis in this case was poor from the outset because of the presence of severe aortic insufficiency and cardiac decompensation, and because of the many emboli to the vessels of the systemic circulation. An apparently successful course of combined therapy was followed by a recrudescence of symptoms twenty-eight days later, due either to bacteriologic relapse (not confirmed by the blood cultures) or to an extensive pelvic infarct or phlebitis. There were signs indicative of possible perforation of a leaflet of the aortic valve. Death resulted from progressive refractory cardiac failure although the infection was apparently controlled. This patient is considered a possible relapse successfully treated from the standpoint of control of the infection.

CASE VI. *Enterococcal endocarditis and chronic rheumatic valvulitis.* (Fig. 4.) W. L., a forty-seven year old white male, was admitted to the Second Medical Division (Cornell) of Bellevue Hospital on March 10, 1948. The patient was a known heroin addict who stated that he had refrained from taking heroin for the past ten years. Three months prior to admission, however, he again began intravenous injections without observing precautions for asepsis. Three weeks prior to admission the patient developed a cough which persisted and became productive of blood-tinged sputum. A week later he noted the onset of exertional dyspnea, orthopnea and ankle edema, all of which increased in severity until the time of admission. There was no history of rheumatic fever.

On admission to Bellevue Hospital the patient was a poorly nourished man who was orthopneic. The temperature was 101.6°F., pulse rate 100, respiratory rate 24 and blood pressure 140/65

mm. Hg. The skin was pale and the veins were distended. There was emphysema and many crepitant rales were heard throughout both lungs. The heart was enlarged to the left anterior axillary line and was in normal sinus rhythm. The first sound at the apex was accentuated and there were murmurs characteristic of mitral stenosis and insufficiency, and of aortic stenosis and insufficiency. A systolic thrill was felt over the neck vessels. The spleen was not palpable, but the abdomen was difficult to examine because of the presence of ascites. The liver was enlarged two finger-breadths below the costal margin. There was edema of the sacral area and of the legs below the knees.

The hemoglobin was 10.5 gm. per cent and there were 4.3 million erythrocytes and 6,000 leukocytes per cu. mm. The urine contained two-plus albumin, 10 to 20 leukocytes and an occasional erythrocyte. Culture of the sputum revealed type XII pneumococcus, beta-hemolytic streptococcus and non-hemolytic streptococcus alpha. Roentgenogram of the chest showed a globular heart, left perihilar consolidation and a small interlobar effusion on the right. An electrocardiogram revealed sinus tachycardia and some signs indicative of left ventricular strain.

The patient was begun on penicillin on March 12th, receiving 100,000 units every six hours intramuscularly. Because the response was poor penicillin was increased on March 19th to 100,000 units every two hours (daily total 1.2 million units); and again on March 22nd to a daily total of 2.4 million units.

The presence of Streptococcus zymogenes bacteremia was demonstrated by blood cultures on March 18th, 20th, 22nd, 25th and 27th. The strain isolated was inhibited *in vitro* by 5 but not by 2.5 units of penicillin per cc., or by 15 but not by 7.5 mcg. of streptomycin per cc. On March 29th when it became apparent that the patient was not responding to 2.4 million units of penicillin, the dosage was increased to a daily total of 4 million units and while on this regimen a sterile blood culture was obtained. On April 5th combined therapy with 6 million units of penicillin and 2 gm. of streptomycin daily was begun. (Fig. 4.) However, the patient's cardiac failure did not respond adequately to adjuvant oxygen, digitalis, salt restriction and mercurials and on April 7th, two days after the institution of combined therapy, he died in severe pulmonary edema. No blood cultures were obtained subsequent to the commencement of combined therapy. A postmortem examination was not performed.

Comment. This patient's illness was complicated by pneumonia and/or pulmonary infarction plus severe cardiac decompensation. His prognosis was, therefore, poor from the outset. Death was the result of both cardiac failure and failure to control the infection. Bacteremia was reversed only on the twenty-sixth hospital day after the daily penicillin dosage had been increased to 4 million units. Combined therapy with penicillin and streptomycin was begun only forty-eight hours before death so that conclusions as to its efficacy are impossible. This case is included primarily to illustrate the failure of relatively large doses of penicillin to control such an infection.

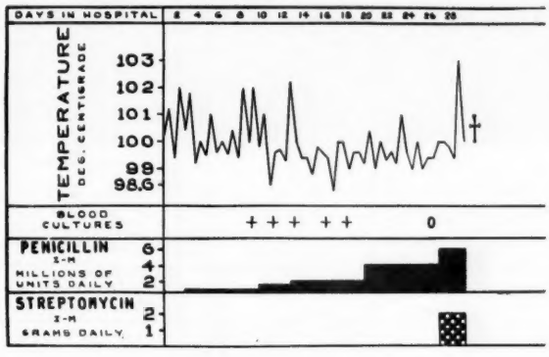


FIG. 4. Case VI. W. L., a white male age forty-seven, with enterococcal endocarditis and chronic rheumatic valvulitis. Increasingly large doses of penicillin failed to arrest the infection; combined penicillin and streptomycin therapy instituted only pre-terminally; course complicated by cardiac failure. Result may be contrasted with that in Case III (Fig. 3).

CASE VII. *Enterococcal endocarditis and chronic rheumatic valvulitis.* (Fig. 5.) S. D., a thirty-four year old white housewife, was admitted to the New York Hospital on October 30, 1948. One year prior to admission the patient noted the gradual onset of painful elbow joints and of ankle edema. Approximately at that time the patient entered upon her fourth pregnancy. In February, 1948, (nine months prior to admission) she experienced a sudden sharp pain in the chest and left side. Her oral hygiene was poor and several teeth were extracted.

The patient was hospitalized a short time in Western Germany because of an enlarged and tender spleen but no treatment was given. She continued to become more seriously ill, developing dyspnea, further ankle edema, productive cough, anorexia, weight loss and signs of an embolus to the right forearm. She was again admitted to a hospital in Germany where the diagnosis of subacute bacterial endocarditis was established by means of blood cultures which were positive for a streptococcus, said to be inhibited *in vitro* by 2.5 units of penicillin per cc. The patient received therapy for cardiac decompensation and anemia, and penicillin was given in doses ranging from 1 million to 8 million units daily for three months without eradication of the infection, although blood cultures were temporarily negative. She delivered a normal child in July, 1948, and a few days postpartum suffered a cerebral embolus. At this time streptomycin was given in dosage of 1 to 4 gm. daily for eight days but abandoned because of the appearance of a rash. The patient returned to the United States and was hospitalized at another hospital where cardiac failure, hepatosplenomegaly and bacteremia were again present. Penicillin, in doses up to 8 million units daily, at one time supplemented with carinamide, was administered with only suppressive effect upon the infection. The patient was transferred to the New York Hospital.

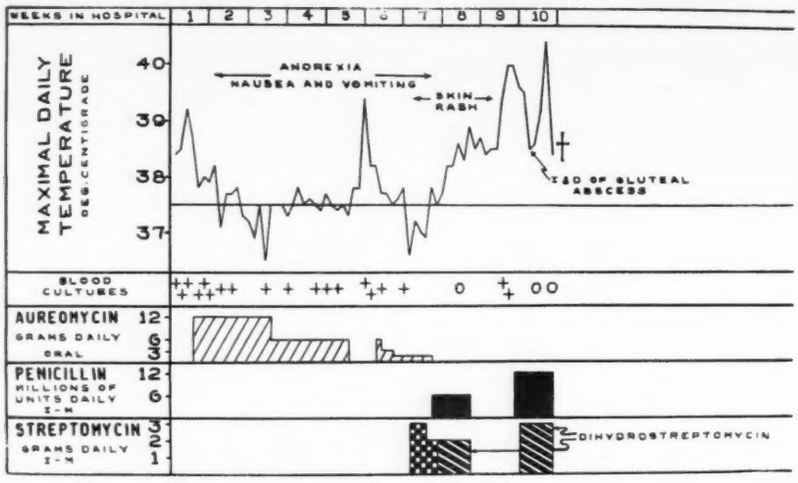
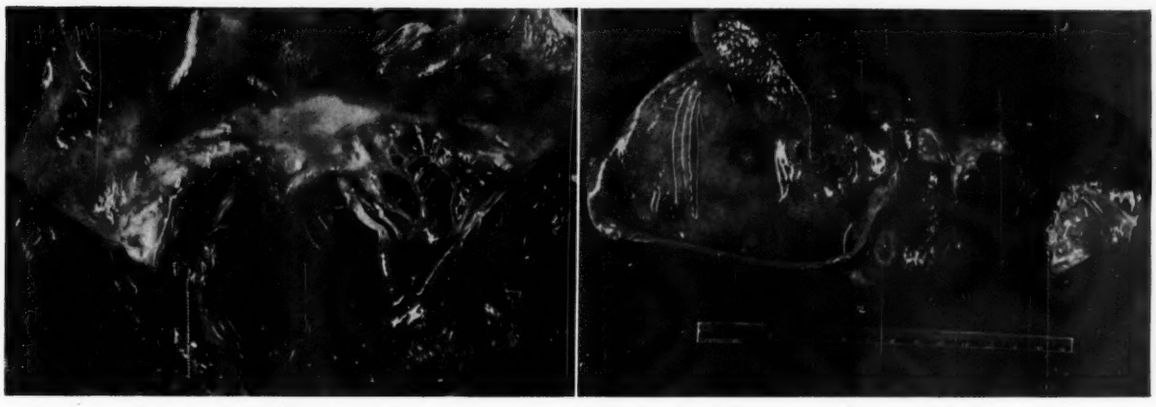


FIG. 5. Case VII. S. D., a white female age thirty-four, with enterococcal endocarditis of mitral valve of long duration. Intensive course of aureomycin failed to reverse bacteremia. Bacteremia reversed by two brief courses of combined penicillin and streptomycin therapy; course complicated by severe inanition, hypersensitivity to streptomycin and splenic abscesses.

On examination the patient was an extremely emaciated female who appeared both acutely and chronically ill. The temperature was 38.5°C., pulse rate 108, respiratory rate 28 and blood pressure was obtained with difficulty as 80/70 mm. Hg. No blood pressure was obtainable in the right arm. The skin was pale, dry and atrophic. There was edema of the legs, sacrum and buttocks. There were many abscesses in the buttocks. There was clubbing of the fingers and toes. The teeth were in poor repair. Moist rales were present at both lung bases. The heart was enlarged 12 cm. to the left of the mid-sternal line and was in auricular fibrillation. The heart sounds were of poor quality, the second pulmonic sound being accentuated. There was a loud harsh systolic murmur over the precordium, most prominent over the apex, and a short harsh diastolic murmur at the apex. A systolic murmur considered distinct from the apical one was heard over the lower end of the sternum. The liver was enlarged to the umbilicus but did not pulsate. The spleen was extremely large, extending to the umbilicus, and was very firm and tender.

The blood contained 9.5 gm. hemoglobin per 100 cc., 3.6 million erythrocytes per cu. mm. and 9,500 leukocytes per cu. mm., with 34 per cent band forms. The urine sediment contained 1 to 2 erythrocytes and 5 to 10 leukocytes per high power field. The blood urea nitrogen concentration was 9 mg. per cent and the A/G ratio was 3.0/2.6. Roentgenographic examination of the chest confirmed the presence of generalized cardiac enlargement. The electro-



6A 6B

FIG. 6. A, the mitral valve from patient S. D. (Case VII) exposed postmortem to show vegetations, fibrosis and thickening. Microscopically the vegetations contained masses of cocci, inflammatory cells and recent as well as old fibrous tissue. B, sagittal section of the spleen from same patient postmortem. The large circular mass on the left is an encapsulated abscess 12 cm. in diameter. Enterococci were grown from the contents. On the right is another smaller abscess.

cardiogram revealed auricular fibrillation, right axis deviation and low QRS complexes throughout all leads.

Blood cultures were repeatedly positive for a non-hemolytic streptococcus, 70–100 colonies per cc. This organism was an enterococcus which was inhibited *in vitro* by 6 but not by 5 units of penicillin per cc.; by 22 but not by 16 mcg. of streptomycin per cc.; or by 0.2 but not by 0.1 mcg. of aureomycin per cc.

The patient was started on aureomycin on November 2nd, receiving 1.5 gm. orally every three hours (daily total of 12 gm.) She received this dosage for fourteen days, experiencing considerable anorexia, nausea and vomiting. Blood cultures continued to be positive although the number of organisms diminished and as long as fourteen days incubation was required for the appearance of growth. On the fourteenth day, because of the attendant gastric distress, aureomycin was reduced to a daily total of 6 gm. and continued for fourteen more days, during which time blood cultures continued positive, 1 to 3 colonies per cc. Aureomycin was administered for a total of twenty-eight days, and during this period the patient, receiving an ancillary regimen of salt restriction, digitoxin and mercuhydrin, exhibited some clinical improvement. The temperature subsided slowly to normal levels, the edema diminished and there was some decrease in the size and tenderness of the liver and spleen. Aureomycin was discontinued on November 30th. Forty-eight hours after the discontinuance of aureomycin, however, fever reappeared and the blood culture was again strongly positive, containing 106–116 colonies per cc. On December 5th the patient was replaced on aureomycin, 4 gm. daily, but this was reduced twenty-four hours later to an approximate daily total of 3 gm. There was subsidence of fever upon this therapy but bacteremia continued. Streptomycin, 3 gm. daily, was added on December 11th, after a test dose of 0.1 gm. which caused no reaction. Three days after beginning streptomycin the patient developed a diffuse, pruritic, maculopapular eruption which was not controlled by pyribenzamine. Streptomycin was reduced to 2 gm. daily and on December 15th aureomycin was discontinued for the second time. Penicillin, 6 million units daily, was started and the next day dihydrostreptomycin was substituted for streptomycin in the hope that the patient, although apparently sensitive to streptomycin, might not react so to the derivative. During this period in the patient's course, she exhibited episodes of acute psychosis, believed to be the result of strain of her long illness and to her severe physical inanition. Because of continuing severity of the skin rash while on combined penicillin and dihydrostreptomycin therapy, all chemotherapy was discontinued on December 22nd, the eighth day of combined treatment. On December 20th while on combined therapy, a sterile blood culture was obtained. Following cessation of all antimicrobial therapy the patient's condition remained fairly stable for six days. On December 28th fever increased sharply and blood cultures on that day and again the following day demonstrated bacteremia, 6 to 14 colonies per cc. Combined therapy was recommenced on December 30th and continued until

the patient expired on January 7, 1949. On January 3rd and 6th blood cultures were again sterile. The patient exhibited a severe psychosis manifested by delirium, hallucinations and catatonia during the last days of life. The enterococcus isolated on December 28, 1948 was compared *in vitro* with that isolated on October 31, 1948 (prior to aureomycin therapy) and the minimal inhibitory concentration of aureomycin had not changed.

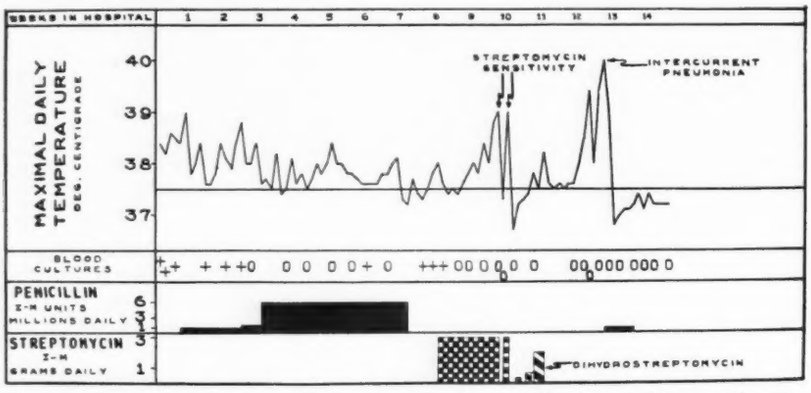


FIG. 7. Case VIII. R. S., a white male age sixty, with subacute bacterial endocarditis caused by a highly penicillin-resistant non-hemolytic streptococcus. Bacteriologic relapse occurred during the administration of 6 million units of penicillin daily. Arrest of the infection followed a twelve-day course of streptomycin; no combined therapy given.

Postmortem examination revealed several large, friable, yellow and red vegetations on the leaflets of the mitral valve. (Fig. 6A.) Microscopically the vegetations contained masses of cocci, polymorphonuclear and mononuclear leukocytes and some recent as well as old fibrous tissue. The spleen contained an encapsulated mass 12 cm. in diameter filled with green purulent material, and several smaller pyramidal lesions of a similar nature. (Fig. 6B.) Smears of the contents of the large abscess revealed numerous gram positive cocci. There were multiple recent and old infarcts of the kidneys and lungs. Enterococci were cultured from both the mitral vegetations and the splenic abscesses.

Comment. This patient received large amounts of penicillin for many months with suppressive effect upon but never arrest of the infection. Aureomycin, apparently the most potent agent by *in vitro* test, was administered in high dosage for a period of twenty-eight days and yet failed to reverse bacteremia. The role of combined therapy in this case is difficult to assess. As in Case VI it was instituted only shortly before death. The most that can be said is that all blood cultures taken during combined penicillin and streptomycin therapy were sterile, whereas this was never the case while the patient was receiving aureomycin alone or aureomycin with streptomycin. (Fig. 5.)

On admission to the New York Hospital the patient's nutritional state was poor. Cardiac failure, however, was well controlled, and it is reasonable to believe that if effective antimicrobial therapy had been introduced at the outset, recovery might have been achieved. The presence of splenic abscesses, seen not infrequently in this disease, possibly contributed to the refractoriness of the infection and it is conceivable that splenectomy could have improved the chances of recovery.

CASE VIII. *Subacute bacterial endocarditis due to a highly penicillin-resistant non-hemolytic streptococcus; and chronic rheumatic valvulitis.* (Fig. 7.) R. S., a sixty year old white male hotel clerk, was admitted to the New York Hospital on January 11, 1947. At the age of ten the patient had had rheumatic fever. Following that he had limited his physical activity, and up to the onset of the present illness had had no symptoms referable to the cardiovascular system. Nine months prior to admission the patient began to experience night sweats, easy fatiguability, anorexia and weight loss. All of his teeth were extracted four months before admission. Two weeks before admission he experienced an attack of sudden

substernal pain and dyspnea which lasted a few minutes. He was forced to go to bed because of the increasing severity of his illness.

On admission to the New York Hospital the patient appeared chronically and acutely ill, exhibiting considerable weight loss. The temperature was 38.4°C., pulse rate 80, respiratory rate 22 and blood pressure 132/68 mm. Hg. There was moderate sclerosis of the retinal vessels. The heart was enlarged 12 cm. to the left of the mid-sternal line but was in normal sinus rhythm. There were classical systolic and presystolic murmurs at the apex, and systolic and diastolic murmurs over the aortic area. There was a presystolic thrill at the apex and a systolic thrill over the aortic area. The liver was enlarged 1 cm. and the spleen 3 cm. below the costal margin. The hemoglobin concentration was 9.9 gm. per cent, erythrocytes 3.4 million per cu. mm. and leukocytes 2.7 thousand per cu. mm., with 31 mature polymorphonuclears, 37 band forms and 26 lymphocytes. The urine contained a slight trace of albumin and an occasional leukocyte. Roentgenographic examination of the chest revealed marked general enlargement of the heart with predominance of the left chamber, pulmonary congestion and multiple "disc atelectases." The electrocardiogram exhibited left axis deviation, prolongation of the P-R time and depression of the S-T segments.

Blood cultures taken the day of admission and daily thereafter were consistently positive for a non-hemolytic streptococcus, 1 to 6 colonies per cc. This organism was found to be heat-resistant and was inhibited *in vitro* by 6 but not by 5 units of penicillin per cc., or by 3 but not by 2 mcg. of streptomycin per cc. It exhibited all of the properties of the enterococcus group except for its failure to ferment mannite and to react with Lancefield Group D antiserum.

On January 15, 1947, the patient was begun on intramuscular penicillin receiving 1.2 million units daily. On January 27th this dosage was increased to 1.8 million units daily. During this therapy blood cultures were repeatedly positive so that on January 31st the penicillin was increased to 6 million units daily. This dosage was continued for twenty-eight days. While on this regimen the patient improved clinically and there were several sterile blood cultures. On the twenty-second day of this course of therapy, however, a blood culture was again positive. Consistent bacteremia reappeared on the third day after cessation of penicillin and remained until the institution of streptomycin therapy. Streptomycin, 3 gm. daily intramuscularly, was started on March 6, 1947. A blood culture drawn twenty-four hours after the institution of streptomycin therapy was positive but all cultures taken thereafter were sterile. Streptomycin was discontinued because of the development of fever and a rash after twelve days of therapy. Purified streptomycin sulfate was administered a day later in the same dosage, but the patient exhibited the same reaction so that it was discontinued. Accordingly, on March 23rd dihydrostreptomycin in small doses was begun. This drug was administered for two days without signs of toxicity. The patient's hospital course thereafter was characterized by steady improvement interrupted only by an intercurrent pneumonia which responded immediately to usual doses of penicillin. Blood cultures were repeatedly sterile after March 8th.

The patient has been seen at frequent intervals since discharge from the hospital and has remained free of any recurrence for twenty-one months. The infection is considered to be arrested.

Comment. This case again illustrates the fact that six million units of penicillin a day for twenty-eight days will not alone control such an infection. Arrest of the infection resulted from twelve days of streptomycin treatment following the unsuccessful course of penicillin. No penicillin was administered during the period of streptomycin therapy. This case is, therefore, not one in which arrest can be attributed to combined therapy. It is included, however, because of the similarity of the therapeutic problem to that presented by the others in this report, even though the infecting organism was not a Lancefield Group D streptococcus. The strain did possess many of the properties of the enterococci and was demonstrated to be highly penicillin-resistant *in vitro*. The streptomycin resistance of the strain is, however, unusually low for this group of organisms and may partially explain the favorable outcome of such a short course of streptomycin. The close succession of the period of streptomycin administration upon the course of penicillin may also have been

TABLE I

SUMMARY OF DATA ON EIGHT PATIENTS INCLUDED IN THIS REPORT

Case	Race, Sex and Age	Clinical Diagnosis	Probable Portal of Entry	Duration of Illness	Organism	*In vitro* Penicillin Sensitivity* (units/cc.)	*In vitro* Streptomycin Sensitivity† (mcg./cc.)	Treatment: Drugs	Treatment: Amount (daily total)	Duration (days)	Results	Comment
I H. B.	W, M, 60	Subacute bacterial endocarditis; heart disease of undetermined type; urethral stricture	Urinary tract (urethral soundings)	4½ mo.	Enterococcus	6	8	Combined‡ { Penicillin / Streptomycin	6 million units / 2 gm.	28	Arrest	Well after 15 months' follow-up
II I. T.	W, M, 57	Subacute bacteremia and probable endocarditis; urinary tract infection	Urinary tract (cystoscopy)	6 wk.	Enterococcus	6	22	Combined { Penicillin / Streptomycin	6 million units / 2 gm.	40	Arrest	Well after 12 months' follow-up
III S. I.	W, M, 45	Subacute bacterial endocarditis; chronic rheumatic valvulitis	Unknown	1 mo.	Enterococcus	4	16	Combined { Penicillin / Streptomycin	6 million units / 2 gm.	42	Arrest	Well after 6 months' follow-up
IV M. T.	W, F, 35	Subacute bacterial endocarditis; chronic rheumatic valvulitis	Septic abortion	2 mo.	Enterococcus	5	8	Combined { Penicillin / Dihydrostreptomycin	6 million units / 2 gm.	40	Arrest	Well after 4 months' follow-up
V A. R.	W, F, 29	Subacute bacterial endocarditis; chronic rheumatic valvulitis; chronic pelvic inflammatory disease	Septic abortion	3 wk.	Enterococcus	3	44	Combined { Penicillin / Dihydrostreptomycin	6 million units / 2 gm.	42	Reversal of bacteremia ? relapse	Death due to cardiac failure. ? perforated aortic leaflet; infection controlled; no autopsy
								Combined { Penicillin / Dihydrostreptomycin	6 million units / 2 gm.	29	Death	
VI W. L.	W, M, 47	Subacute bacterial endocarditis; chronic rheumatic valvulitis; heroin addiction	Septic intravenous injections (heroin)	3 wk.	Enterococcus	5	15	Penicillin	1.2–2.4 million units	10	Death	Combined therapy only 3 days pre-terminally; no autopsy
								Penicillin	4 million units	8		
								Combined { Penicillin / Streptomycin	6 million units / 2 gm.	2		
VII S. D.	W, F, 32	Subacute bacterial endocarditis; chronic rheumatic valvulitis	Tooth extractions? pregnancy?	9–12 mo.	Enterococcus	6	22	Aureomycin	6–12 gm.	28	Failure; death	Autopsy: partially healed endocardial vegetations and large splenic abscesses; combined therapy of short duration
								Combined { Penicillin / Dihydrostreptomycin	6 million units / 2 gm.	6		
								Combined { Penicillin / Dihydrostreptomycin	12 million units / 3 gm.	7		
VIII R. S.	W, M, 60	Subacute bacterial endocarditis; chronic rheumatic valvulitis; arteriosclerosis	Tooth extractions	3 mo.	Non-hemolytic streptococcus	6	3	Penicillin	6 million units	28	Failure (relapse)	No combined therapy; course of streptomycin pursuant to unsuccessful course of penicillin; 21 months' follow-up
								Streptomycin	3 gm.	12	Arrest	

* Determined by staggered serial tube dilution series, using plain beef heart infusion broth containing 2% rabbit blood; incubation at 37°C. for 48 hours.

† Determined by staggered serial tube dilution series, using "F.D.A." broth containing no blood; incubation at 37°C. for 48 hours. Values obtained by testing in plain infusion broth (higher salt content and lower pH), or in broth containing blood, were appreciably higher.

‡ The term "combined" refers to the concurrent administration of the two antimicrobials.

a factor in that the bacterial population almost certainly had been reduced in numbers by the penicillin, and raises the possibility that the successive use of antimicrobial agents might be as effective as their concurrent use. This patient's course is also an illustration of the fact that patients who exhibit hypersensitivity to streptomycin may sometimes receive the dihydro derivative without reaction.

The clinical features of the eight cases in this report are presented in Table I. The results of therapy in the seven cases of enterococcal endocarditis and bacteremia are summarized in Table II. It may be seen that of the five patients completing a course of combined therapy of reasonable duration, the infection was controlled in all five, four were cured and one died following retreatment for a questionable relapse.

TABLE II

RESULTS IN PATIENTS RECEIVING COMBINED PENICILLIN AND STREPTOMYCIN THERAPY FOR ENTEROCOCCAL ENDOCARDITIS

	No.	Died with Infection Uncontrolled	Died with Infection Apparently Controlled	Total Died	No. "Cured"	"Cured" Per cent	Relapsed
All patients regardless of duration of treatment	7	2	1	3	4	57	1(?)
Patients who completed 28–42 day course	5	0	1	1	4	80	1(?)

TABLE III

BIOLOGIC PROPERTIES OF STREPTOCOCCI ISOLATED FROM THE BLOOD STREAMS OF PATIENTS IN THIS REPORT

Case Number	Species* Name	Hemolysis on Blood Agar†	Soluble Hemolysin	Resistant to 60°C. for 30 Minutes	Growth at 10°C.	Growth in 6.5% NaCl Broth	Hydrolysis of Mannite	Liquefaction of Gelatin	Serologic Group (Lancefield)‡	Dextran§ Production	Minimal Inhibitory Concentrations *in vitro*‖		
											Penicillin units/cc.	Streptomycin micrograms/cc.	Aureomycin microgram/cc.
I	Streptococcus fecalis	Indifferent	0	+	+	+	+	0	D	0	6	8	0.8
II	Streptococcus zymogenes	Beta	+	+	+	+	+	+	D	0	6	22	0.8
III	Streptococcus fecalis	Indifferent	0	+	+	+	+	0	D	0	4	16	0.8
IV	Streptococcus liquefaciens	Alpha	0	+	+	+	+	+	D	0	5	8	0.4
V	Streptococcus zymogenes	Alpha	+	+	+	+	+	+	D	0	3	44	0.4
VI	Streptococcus zymogenes	.....	..	+	..	..	..	+	..	..	5	15	...
VII	Streptococcus fecalis	Indifferent	0	+	+	+	+	0	D	0	6	22	0.2
VIII	None applicable	Indifferent	0	+	+	+	0	0	Did not group in any serum	0	6	3	0.1

* Based on the classification of Homer F. Swift in Bacterial and Mycotic Infections of Man, Chap. 11. Edited by R. J. Dubos. J. B. Lippincott Co.

† 5% horse blood agar; horse blood generally resulted in more brilliant greening but less pronounced beta hemolysis than occurred on rabbit blood agar.

‡ Performed through the courtesy of Dr. Robert Watson, Dept. of Medicine, Cornell University Medical College.

§ Performed through the courtesy of Dr. Edward Hehre, Dept. of Bacteriology, Cornell University Medical College.

‖ Minimal inhibitory concentrations *in vitro* were determined by the use of staggered serial dilution series. Those for penicillin were performed in a routine beef-heart infusion broth containing 2 per cent rabbit blood; incubation at 37°C. for forty-eight hours. Those for streptomycin were performed in a peptone broth of pH 7.5–8.0 and 2.5 per cent sodium chloride concentration (Stebbins and Robinson. *Proc. Soc. Exper. Biol. & Med.*, 59: 255, 1945) without the addition of blood; incubation at 37°C. for forty-eight hours. (The values after twenty-four hours' incubation were approximately half of those values listed.) Those for aureomycin were performed in routine infusion broth containing 2 per cent rabbit blood; incubation at 37°C. for eighteen to twenty-four hours. If a medium of higher salt content or of lower pH was employed or if blood was added, the minimal inhibitory concentration of streptomycin was appreciably higher. If incubation was prolonged to forty-eight hours, the minimal inhibitory concentration of aureomycin invariably rose to 6 to 25 mcg./cc. A 10^{-4} dilution of an 18–24 hour culture was employed as bacterial inoculum in all tests.

IN VITRO OBSERVATIONS

1. *Studies on Biologic Properties of Strains of Streptococcus Isolated from the Blood Streams of Patients in This Report.* Freshly isolated or frozen and dried cultures of the streptococci isolated from the blood of the patients in this report were available in all instances except Case VI. These cultures were subjected to a series of laboratory tests in order to define more completely their bacteriologic properties. The results are presented in Table III.

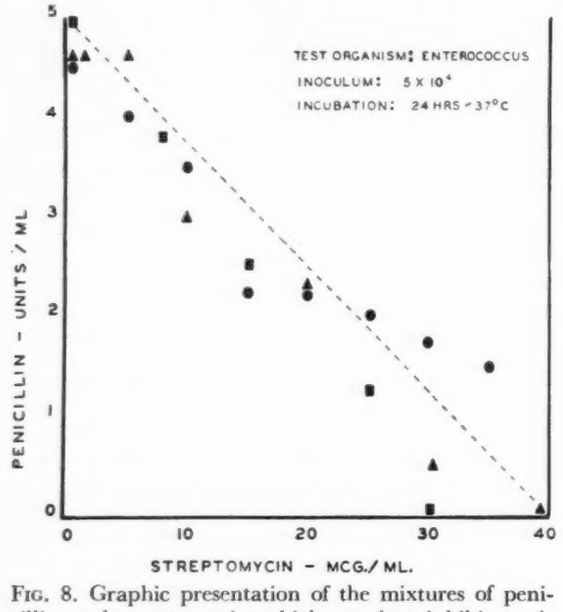


FIG. 8. Graphic presentation of the mixtures of penicillin and streptomycin which are just inhibitory *in vitro* for a strain of enterococcus. Composite values derived from three separate experiments. The linear distribution of the points, indicating total positive summation, is apparent.

2. *Studies on the Combined Effect of Penicillin and Streptomycin on the Enterococcus in vitro.* In an attempt to elucidate the apparent greater efficacy of combined therapy than of massive single drug therapy in this infection, a series of *in vitro* experiments was carried out. Employing the hemolytic enterococcus recovered from patient I. T. (Case II) as test organism, multiple staggered serial dilutions containing known mixtures of penicillin and streptomycin in beef-heart infusion broth were constructed. Each tube was inoculated with a constant number of bacteria and after incubation at 37°C. for twenty-four hours the tubes were examined for gross turbidity. The results of a typical experiment are presented in Table IV. As may be seen in this table, with each progressive decrease in concentration of either drug, a like increase in concentration of the other proved inhibitory.

The results of three separate experiments of this nature are plotted in graphic form in Figure 8. The triangles represent the just-inhibitory mixtures from the data in Table IV; the dots and squares from two other similar experiments. It may be seen that a concentration of penicillin alone of 4.5–5 units per cc. was effectively inhibitory for this organism. Similarly, a concentration of streptomycin alone of 30 to 40 micrograms per cc. was sufficient to prevent growth. If a streptomycin concentration of 5 micrograms per cc. was present, the penicillin concentration required to prevent growth was reduced to 4.0–4.5 units per cc. If the streptomycin concentration was increased to 10 micrograms per cc., the required penicillin concentration fell to 3.0–3.5 units per cc.; and in the presence of 20 micrograms of streptomycin per cc. a penicillin concentration of 2.25 units per cc. was effectively inhibitory.

TABLE IV
GROWTH OF AN ENTEROCOCCUS IN MIXTURES OF PENICILLIN AND STREPTOMYCIN—INCUBATION AT 37°C. FOR TWENTY-FOUR HOURS

Streptomycin Conc. (micrograms per cc.)	Penicillin Concentration (units per cc.)								
	6	4.5	3	2.25	1.5	1.13	0.75	0.56	0
0	0	0	+	+	+	+	+	+	+
1	0	0	+	+	+	+	+	+	+
5	0	0	+	+	+	+	+	+	+
10	0	0	0	+	+	+	+	+	+
20	0	0	0	0	+	+	+	+	+
30	0	0	0	0	0	0	0	0	+
40	0	0	0	0	0	0	0	0	0

Five units per cc. is the concentration of penicillin which may be considered 100 per cent inhibitory for this enterococcus under test conditions, and 40 micrograms per cc. the concentration of streptomycin which may be considered 100 per cent inhibitory. Then a mixture of 2.5 units of penicillin per cc. and 20 micrograms of streptomycin per cc., an effectively inhibitory mixture, contains 50 per cent of the inhibitory concentration of each of the two

components. Similarly, other mixtures demonstrated to be just effective in preventing growth contained fractions of the inhibitory concentration of each drug the sum of which equalled, or closely approximated, one. Fractionally inhibitory concentrations of the two drugs, the algebraic sum of which equalled less than one, were occasionally found effective but only within the range of experimental variation.

The experimental values plotted in Figure 8 may be seen to approximate closely a line joining the 100 per cent inhibitory concentration of penicillin alone and of streptomycin alone. This line is the curve along which points would fall if there were complete positive summation of subinhibitory concentrations (synergism*). Points falling within the triangle formed by the axes and the broken line would be indicative of potentiation (super-summation), and those falling above the line would be indicative of incomplete summation or of no summation at all.

REMARKS

Five to 10 per cent of all cases of subacute bacterial endocarditis are caused by enterococci, organisms very highly resistant to penicillin. The treatment of these patients with penicillin, even in massive amounts, has been generally unsuccessful, although occasional cases have been arrested following the administration of great amounts over long periods of time.

Enterococci are relatively more sensitive *in vitro* to streptomycin than to penicillin. The limited experience thus far with the use of streptomycin in the treatment of this disease, however, has not been promising. Consequently, the results set forth in this report on the treatment of seven patients with concurrent penicillin and streptomycin are considered encouraging.

In two instances (Cases VI and VII) combined therapy was instituted only at a very late date in the course of the patient's illness, after other forms of therapy had failed. Both patients were in extremely poor general condition at the time combined therapy was commenced. One patient presented refractory cardiac failure and the other extreme inanition and toxic psychosis. Both patients succumbed soon after the institution of combined therapy. In neither instance can any conclusion be reached as to the efficacy of combined treatment, except that all blood cultures (three in number) taken while patient S. D. (Case VII) was receiving penicillin and streptomycin were sterile. This was never accomplished during a long period of aureomycin administration in high dosage. Neither Case VI nor Case VII, therefore, can be considered a failure of combined therapy. Indeed, it appears to have been the superior antimicrobial regimen employed in the treatment of patient S. D.

In Cases I to V inclusive the patients all received relatively long courses of combined therapy sufficiently early in the course of the disease so that conclusions as to its efficacy are possible. In all of these cases reversal of bacteremia was prompt, occurring within forty-eight hours after the commencement of therapy in all instances. In none was bacteremia subsequently encountered. One patient (Case III) was in cardiac failure of moderate severity at the time treatment was instituted so that his prognosis was poor, even with the benefit of effective antimicrobial therapy. His recovery, therefore, is in sharp contrast to

* The term *synergism*, as used here, is defined by Goodman and Gilman[21] as a combined effect of two or more drugs (producing similar end results) which is equal to the algebraic sum of their individual effects, i.e., "Positive summation is known as synergism." Thus if one-half the therapeutic dose of drug A and one-half the therapeutic dose of drug B are effective in achieving the desired result, then the phenomenon may be correctly termed positive summation, or synergism. "Synergism," however, has been used by many investigators of antimicrobial drugs in a more general sense, i.e., to be any effect due to a mixture of antibacterial substances which is greater than that attributable to any one of the components of the mixture acting alone. This definition includes, therefore, the results of mixtures containing fractions of the effective amounts of the individual components the sum of which equals more than one. Thus, in common usage the term "synergism" has been applied to incomplete summation as well as complete summation, and has also included the phenomenon of true potentiation (instances in which the combined action of two drugs is greater than that which can be anticipated from the sum of their individual actions, i.e., mixtures containing fractions of effective amounts of the individual components the sum of which equals less than one).

the failure met with in Case VI in which control of the infection was not achieved in spite of the administration of increasingly large amounts of penicillin.

Patient A. R. (Case V) responded excellently to a course of combined therapy of adequate duration. In this case, again, the prognosis was made worse by the presence of cardiac decompensation. The patient re-entered the hospital after a remission of twenty-eight days' duration, possibly in relapse. However, bacteremia was never demonstrated during the second admission. The cardiac failure, associated with aortic insufficiency of an extreme degree and possibly with a perforated aortic leaflet, became increasingly severe and she succumbed primarily as a result of these complications and not because of uncontrolled infection. This case is considered as a possible though doubtful relapse. It is included as such in Table II.

Of the five patients who completed a course of combined therapy of reasonable duration, four were cured and one died following retreatment for a possible relapse but with apparent control of the infection. (Table II.) These results are considered superior to those which could have been expected if either penicillin or streptomycin had been employed alone in the dosages in which they were employed together. They would appear to represent an *in vivo* synergistic* effect of the two antimicrobial agents.

Some elucidation of the possible mechanism of the synergism observed *in vivo* has resulted from *in vitro* experimentation. Evidence has been presented that the combination of penicillin and streptomycin acting on the enterococcus *in vitro* behaves in a truly synergistic manner, i.e., there is complete algebraic summation of partial effects.

The complete positive summation of partially inhibitory concentrations of penicillin and streptomycin upon this organism could be ascribed to one or both of two possible mechanisms, previously postulated by others.[23] The effect observed could be the result of the elimination by the second antibacterial agent of variants in the bacterial population which are hereditarily more resistant to the first; or to the activity of one agent upon organisms "weakened" by the other agent. A third theoretic possibility, that the two drugs combine chemically to form a more potent compound, is entirely unsupported. Of the two above possibilities there is some experimental evidence in support of the second. Spicer and Blitz,[24] working with Streptococcus viridans and enterococci, reported that members of the bacterial population which were not killed by contact with penicillin but were prevented from multiplying exhibited increased sensitivity to a second drug, streptomycin. There is evidence that the increased streptomycin sensitivity of the organisms surviving contact with penicillin is a reversible physiologic condition rather than a hereditarily transmissible property of these cells.[25] Furthermore, there is evidence indicating that these penicillin-exposed cells are also more highly sensitive to antibacterial substances other than streptomycin.[25]

It would seem, then, that a possible mechanism for the summative action of penicillin and streptomycin on the enterococcus *in vitro* and *in vivo* would be the elimination by streptomycin of members of the bacterial population which survive exposure to but are partially inhibited by penicillin.

The clearly excellent response of human enterococcal endocarditis to the concurrent administration of these two drugs might be explained on this basis. Thus although the penicillin concentration of the body fluids well exceeds the minimal inhibitory concentration for the infecting organism (as determined by the usual test) so that many of the bacteria die, there are those which remain viable and are able to resume multiplication following the withdrawal of penicillin. The presence of streptomycin in the body simultaneously with penicillin results in the death of these persisting members of the bacterial population and

* See footnote, page 295.

thus in complete eradication of the parasites so that relapse cannot occur.

It is interesting to speculate upon the place of combined chemotherapy in the future. Conceivably, it may prove an effective means of decisively arresting infections amenable only to suppression or to sporadic arrest by the use of single antimicrobial agents. One instance of this, the combined therapy of brucellosis with streptomycin and sulfonamide, has been demonstrated by Spink and his associates, and the results of the combined therapy of enterococcal endocarditis reported here may represent another example of the value of such therapy.

Experience with the newer antimicrobial agents, aureomycin and chloramphenicol, in the treatment of enterococcal endocarditis is limited. In spite of the relatively high *in vitro* sensitivity to aureomycin displayed by the organism infecting patient S. D. (Case VII) the administration of this drug in high dosage failed to reverse bacteremia. The presence of organisms in the splenic abscesses, however, might have resulted in the ultimate failure of any therapy. There are reports of several patients with enterococcal endocarditis who have received benefit from aureomycin, although relapse accompanied by emergence of a resistant strain has occurred in at least one.[26] In a recently treated patient the concurrent administration of aureomycin and chloramphenicol failed to reverse bacteremia,[17] and in another case the administration of chloramphenical in doses of 2 to 6 gm. daily for four weeks failed to arrest the infection.[27] It must be stated that the place of aureomycin and of chloramphenicol in the treatment of this type of endocarditis is not yet established and further therapeutic trial seems indicated. It is possible that they may find use in combination with either penicillin or streptomycin or with both. It is interesting to speculate on the treatment of choice in patients with enterococcal endocarditis in whom the organisms have been bred to an extremely high streptomycin resistance by inadequate therapy. Such a patient has been observed recently.[17] The efficacy of combined penicillin and streptomycin therapy in such a case remains to be determined.

Patient S. D. (Case VII) was of further interest because of the presence of multiple splenic abscesses demonstrated at autopsy. The propensity for the formation of metastatic abscesses in the course of enterococcal endocarditis has been noted by others.[4,5,6] This is in contrast to the usual course of Streptococcus viridans endocarditis in which gross abscess formation is a distinct rarity, although necrosis within large infarcts, not true suppuration, may occur.[28] Because of the possibility that a large abscess of the spleen or other organ might perpetuate bacteremia and consequently the infection in the heart valves, and because such a focus might be difficult to eradicate by any type or amount of systemic therapy, it would appear that surgery should be seriously considered in cases of enterococcal endocarditis complicated by gross abscess formation. In Case VII it can be postulated that the removal of several large loci of infection by splenectomy could have improved the patient's chances for recovery.

SUMMARY

Results are reported of the concurrent administration of penicillin and streptomycin to seven patients with enterococcal endocarditis. An eighth patient infected with a similar organism is included.

Two of the seven patients received combined therapy for only brief periods prior to death and are not considered as having had adequate trials of therapy. In the remaining five patients results of the combined treatment were striking, permanent arrest of the infection being readily achieved in four. The fifth patient sustained a questionable relapse and subsequently died. However, there was no evidence of uncontrolled infection.

These results are superior to those which have been achieved by the use of penicillin alone. It is believed that this form of therapy represents the treatment of choice for

enterococcal endocarditis and bacteremia at the present time. The results appear to represent a summative (synergistic) effect of the two antimicrobial drugs upon the enterococcus *in vivo*. Evidence for a combined effect *in vitro* is presented and an hypothesis as to the possible mechanism of such an effect is discussed.

The use of combinations of antimicrobial agents appears to offer an effective method of achieving permanent arrest of some infections which can be suppressed only temporarily by the administration of a single drug.

Acknowledgment is made to Miss Carol Adams for technical assistance.

Addendum: Since the preparation of this manuscript two additional patients with enterococcal endocarditis have been treated with concurrent administration of penicillin and streptomycin. One patient was a forty-one year old woman whose infection began eighteen months prior to admission. She had received intensive penicillin therapy followed by a prolonged course of aureomycin without achieving permanent remission of the infection. Relapse had also occurred following a five-week course of combined therapy with 4 million units of penicillin and 1.0 gm. of streptomycin daily. When seen at the New York Hospital the patient was in cardiac failure; blood cultures were positive for an enterococcus inhibited *in vitro* by 6.25 units of penicillin per cc. or 4.0 micrograms of streptomycin per cc. In spite of intensive combined penicillin and streptomycin therapy the patient succumbed after six weeks' hospitalization. Postmortem examination revealed vegetations on the mitral valve, a ruptured chorda tendinae of the mitral valve and extensive mesenteric infarcts. Cultures of the vegetations failed to reveal enterococci.

The second patient, a twenty-three year old female, with an infection of twelve months' duration which had proven refractory to prolonged combined penicillin and aureomycin therapy, responded well to eight weeks of combined penicillin and streptomycin therapy. The patient has been well and blood cultures have been negative seven weeks following discontinuance of therapy. The enterococcus isolated from this patient was inhibited *in vitro* by 6.25 units of penicillin per cc. or by 2.0 micrograms of streptomycin per cc.

REFERENCES

1. Evans, A. C. and Chinn, A. L. The enterococci: with special reference to their association with human disease. *J. Bact.*, 54: 495, 1947.
2. Sherman, J. M. The enterococci and related streptococci. *J. Bact.*, 35: 81, 1938.
3. Sherman, J. M. The streptococci. *Bact. Rev.*, 1: 1, 1937.
4. Rantz, L. A. and Kirby, W. M. M. Enterococcic infections. *Arch. Int. Med.*, 71: 516, 1943.
5. Skinner, D. and Edwards, J. E. Enterococcal endocarditis. *New England J. Med.*, 226: 8, 1942.
6. Wallach, K. Subacute enterococcus endocarditis. *J. Mt. Sinai Hosp.*, 1: 80, 1934.
7. Watson, R. F. Sensitivity of various serological (Lancefield) groups of streptococci to penicillin. *Proc. Soc. Exper. Biol. & Med.*, 57: 65, 1944.
8. Sirota, J. H., Gerber, I. E. and Baehr, G. Chemotherapy of subacute enterococcus endocarditis. *J. Mt. Sinai Hosp.*, 14: 604, 1947.
9. Clark, W. H., Bryner, S. and Rantz, L. A. Penicillin-resistant non-hemolytic streptococcal subacute bacterial endocarditis. *Am. J. Med.*, 4: 671, 1948.
10. Romansky, Monroe. Personal communication.
11. Stuart-Harris, C. H., Colquhoun, J. and Brown, J. W. Penicillin and carinamide in resistant subacute bacterial endocarditis. *Lancet*, 1: 99, 1949.
12. Hunter, T. H. Use of streptomycin in treatment of bacterial endocarditis. *Am. J. Med.*, 2: 436, 1947.
13. Keefer, C. S. and Hewitt, W. L. The Therapeutic Value of Streptomycin. A Study of 3,000 Cases. Pp. 63–65. Ann Arbor, Mich., 1948. J. W. Edwards Co.
14. Cady, J. B. and Allen, W. H. A case of Streptococcus fecalis septicemia treated unsuccessfully with streptomycin. *Guthrie Clin. Bull.*, 16: 31, 1946; Cady, J. C. and Hunter, A. L. Streptococcus fecalis septicemia: concluding report of a case. Ibid., 16: 90, 1947.
15. Boger, W. P., Kay, C. F., Eisman, S. H. and Yeoman, E. E. Carinamide, a compound that inhibits penicillin excretion by the renal tubules, applied to the treatment of subacute bacterial endocarditis. *Am. J. Med.*, 214: 493, 1947.
16. Cressy, N. L., Lahey, W. J. and Kunkel, P. Streptomycin in the treatment of bacterial endocarditis. *New England J. Med.*, 239: 497, 1948.
17. Adcock, J. D. Personal communication.
18. Naegele, C. F. Streptomycin treatment of bacterial endocarditis due to Streptococcus viridans; report of two cases. *Ann. Int. Med.*, 30: 1049, 1949.
19. Zeller, W. W., Hirsh, H., Dowling, H. F., Hussey, H. and Robinson, J. A. The treatment of bacterial endocarditis with penicillin and streptomycin. *M. Ann. District of Columbia*, 17: 21, 1948.
20. Guss, J. H. Successful treatment of subacute bacterial endocarditis with streptomycin. *Am. Heart J.*, 35: 662, 1948.
21. Goodman, L. and Gilman, A. The Pharmacological Basis of Therapeutics. P. 13. New York, 1941. The Macmillan Company.

22. Robbins, W. C. and Tompsett, R. Proceedings of the Second National Symposium on Antibiotics of the National Institutes of Health, Washington, D. C. April 11–12, 1949. Abstract, *J. Clin. Investigation*, 28: 1043, 1949.
23. Robbins, W. J., Kavanagh, F. and Hervey, A. Synergism between some antibacterial substances. *Bull. Torrey Botanical Club*, 75: 502, 1948.
24. Spicer, S. and Blitz, D. A study of the response of bacterial populations to the action of penicillin; a quantitative determination of its effect on the organisms. *J. Lab. & Clin. Med.*, 33: 417, 1948.
25. Robbins, W. C. and Tompsett, R. Unpublished observations.
26. Harvey, J. C., Mirick, G. S. and Schaub, I. G. Clinical experience with aureomycin. Proceedings of the Second National Symposium on Antibiotics of the National Institutes of Health, Washington, D. C. April 11–12, 1949. *J. Clin. Investigation*, 28: 987, 1949.
27. Greenfield, I. Personal communication.
28. Libman, E. and Friedberg, C. K. Subacute Bacterial Endocarditis. P. 26. New York, 1941. Oxford University Press.

Effect of Penicillin and Aureomycin on the Natural Course of Streptococcal Tonsillitis and Pharyngitis*

CAPT. WILLIAM R. BRINK, M.C., CHARLES H. RAMMELKAMP, JR., M.D.,
CAPT. FLOYD W. DENNY, M.C. *and* CAPT. LEWIS W. WANNAMAKER, M.C.
Cleveland, Ohio

THE problem of determining the efficacy of therapy of acute streptococcal infections of the upper respiratory tract is difficult for these infections are of short duration, and are usually not severe. Only by controlled studies in which an attempt is made to quantitate the occurrence of symptoms, physical signs and fever is it possible to conclude that this disease has been affected favorably. The present study was undertaken to determine the relative efficacy of penicillin and aureomycin in the treatment of group A hemolytic streptococcal respiratory infections. For this purpose 475 patients with exudative tonsillitis or pharyngitis were studied by clinical, bacteriologic and serologic methods.

DESCRIPTION OF STUDY

The investigation was conducted at Francis E. Warren Air Force Base, Wyoming, between March 8 and April 30, 1949. During the period of study streptococcal respiratory infections were epidemic with rates of ten to thirteen hospitalized cases per 1,000 men per week.

All patients admitted to the base hospital with respiratory symptoms or fever were examined within a few hours by a physician from the Streptococcal Disease Laboratory. If exudate of any degree was observed on the tonsils or pharyngeal mucosa, the patient was admitted to the study ward. Selection for the treated and control groups was determined by the air force serial number. While penicillin was being evaluated, patients whose serial number ended in an even digit received intramuscular injections of procaine penicillin G in peanut oil with 2 per cent aluminum monostearate. The dosage was 300,000 units on admission, 300,000 units at forty-eight hours and 600,000 units at ninety-six hours. Patients whose serial number ended in an odd digit served as controls and received no treatment.

One week after concluding the study of penicillin aureomycin† therapy was employed. Patients with serial numbers ending in the digits one and three were given no specific treatment. All other patients with exudative tonsillitis and pharyngitis received 1 gm. of aureomycin immediately, then 0.5 gm. every four hours for twenty-four hours and 0.25 gm. every four hours for the next three days. Total dosage was 8.5 gm. in four days.

While in the hospital the patients received no antipyretics but were given small doses of codeine for severe headache. Oral temperatures were taken every four hours. A culture of the pharynx, total leukocyte count and a blood specimen were obtained on admission. The throat cultures were repeated on the second and third hospital days. Leukocyte counts were repeated on the second hospital day. During aureomycin therapy leukocyte counts were also done on the third day and cultures were taken at the time of discharge from the hospital. Three to four weeks after admission to the hospital the patients were examined for

† Supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

* From the Streptococcal Disease Laboratory, Francis E. Warren Air Force Base, Wyoming, and the Department of Preventive Medicine, Western Reserve University, School of Medicine, Cleveland, O. This investigation was supported through the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of The Surgeon General, Washington, D. C.

poststreptococcal complications, and a culture of the throat and a blood specimen were obtained.

The clinical observations were made by two individuals so that comparability of recording could be maintained. All treatment was administered without the knowledge of the physicians studying the cases. The occurrence of symptoms (chilliness, feverishness, headache, malaise, anorexia, nausea, vomiting, chest pain, earache, sneezing, nasal obstruction or discharge, epistaxis, dry and sore throat, hoarseness, cough and skin rash) was recorded by twelve-hour periods for the first forty-eight hours and daily thereafter. Physical signs were recorded daily. Symptoms were graded as being absent, present or severe; physical signs were graded as absent, present or marked. In each instance the exact time of onset of the disease was noted.

Cultures of the pharynx were streaked on agar plates containing horse blood within approximately one hour after collection. After twenty-four hours' incubation at 37°C. the plates were examined and colonies exhibiting beta-hemolysis were transferred to agar plates containing sheep blood for confirmation. Identification of the serologic group was made by the method of Maxted;[1] typing was performed by the technic of Swift, Wilson and Lancefield.[2] Antistreptolysin "O" titers were determined on acute and convalescent sera by a modification of the Swift and Hodge technic.[3]

RESULTS

Patients admitted to the hospital with exudative lesions of the tonsils or oropharynx were placed in treated or control groups according to their air force serial number. There was a total of 198 patients who received no treatment; 197 received penicillin and 80 were treated with aureomycin.

The clinical and laboratory data indicate that the majority of the infections were caused by group A streptococci. These organisms were isolated from the cultures of the throat of 189 of the 198 patients in the control group. The clinical features and the elevated leukocyte counts were compatible with the diagnosis of a streptococcal infection. Finally the fact that an increase of two dilution increments in the antistreptolysin "O" titer was demonstrated in 82 per cent of the sera collected from the control group established the streptococcal etiology of these infections.

Comparability of Treated and Control Groups. The data were first examined to determine whether bias occurred in the selection of the three groups of patients. For this purpose the three groups were compared with respect to the frequency of certain symptoms occurring during the first twelve hours of illness, the presence of abnormal physical signs on admission and certain laboratory data. (Table 1.) The relative frequency of feverishness, headache and loss of appetite was similar in the three groups; sore throat, however, occurred somewhat less frequently in those who received penicillin than in the other two groups. This was also associated with a decreased incidence of tenderness of the cervical lymph nodes in the patients who later received penicillin. There was a distinct difference in the incidence of edema of the soft palate, the control group exhibiting less swelling of the palate and uvula

TABLE 1
COMPARABILITY OF THE TREATED AND CONTROL GROUPS

	Treatment		
	None (198 cases) %	Penicillin (197 cases) %	Aureomycin (80 cases) %
Symptoms:			
Feverishness*	80	74	78
Headache*	76	79	79
Anorexia*	76	78	75
Sore throat*	88	81	91
Physical signs:			
Tender cervical nodes†	76	69	79
Edema of soft palate†	52	63	71
Scarlet fever	2	1	1
History of tonsillectomy	29	28	29
Age 17–21	84	86	80
Laboratory:			
Leukocyte count above 12,000	76	70	79
Streptococcus			
Type 5	29	27	31
Type 14	26	25	39
Type 24	20	24	5

* Present during first 12 hr. of illness.
† Physical signs present during first day of illness.

than the group receiving aureomycin or penicillin.

There was a difference in the type distribution of the group A streptococci isolated from the throat cultures in the three groups of patients. Type 24, which caused 20 and

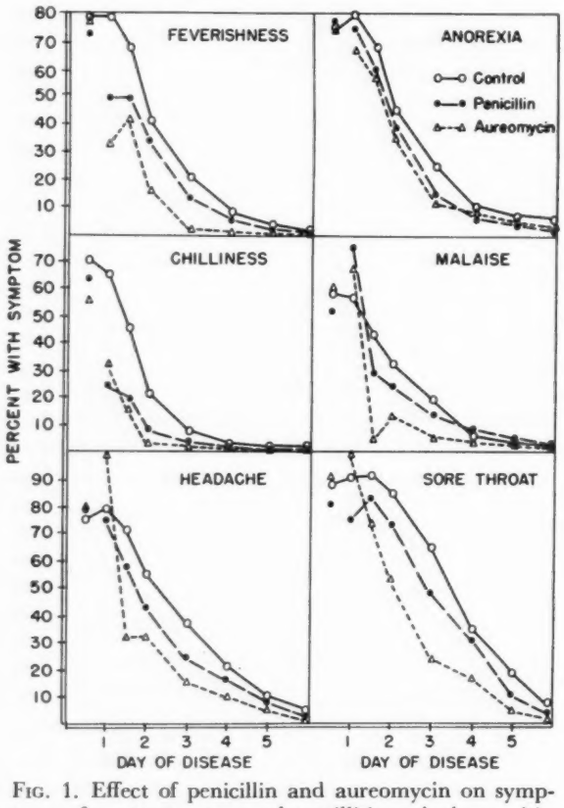


FIG. 1. Effect of penicillin and aureomycin on symptoms of acute streptococcal tonsillitis and pharyngitis.

24 per cent of the infections in the untreated patients and those who received penicillin, respectively, caused only 5 per cent of the illnesses in those receiving aureomycin. Because of these differences an analysis was made of the natural course of the illness in fifty-four patients with type 5 infections, forty-nine patients with type 14 and thirty-seven cases of type 24 infection in the control group. These tabulations showed that type 24 streptococci were associated with a somewhat milder disease than that caused by the other two types. This may explain the higher incidence of sore throat, tender cervical lymph nodes and edema of the soft palate in those patients who subsequently received aureomycin. Since a relatively large number of patients who received no treatment or penicillin therapy were infected with type 24 streptococci, the patients in these two groups would tend to recover more rapidly than those patients receiving aureomycin.

Effect on Symptoms and Physical Signs. The effect of penicillin and aureomycin treatment on selected symptoms is recorded in Figure 1. The symptoms were tabulated with reference to the time of onset of the disease. The first points in each figure indicate the prevalence of the symptom before institution of therapy. Penicillin or aureomycin treatment resulted in a more rapid disappearance of symptoms than occurred in the control group of patients. Aureomycin was more effective than penicillin although the differences were not marked. The prevalence of anorexia was about equal in the three groups throughout the period of observation. Nausea and vomiting were especially prevalent among those patients receiving aureomycin, 51 per cent having these complaints. In the untreated group 35 per cent complained of nausea or vomiting during the course of the illness. Loose stools occurred in 45 per cent of the patients receiving aureomycin whereas only 15 per cent of the control group exhibited this symptom.

Treatment instituted early in the course of illness resulted in a more rapid recovery than when therapy was delayed. The effect of early treatment on the symptom, sore throat, is shown in Figure 2. Patients treated with aureomycin within the first twenty-four hours of onset of illness no longer complained of sore throat after the fourth day whereas on the sixth day 8 per cent of the control group still had this symptom. Penicillin therapy instituted after the first twenty-four hours of illness resulted in only a slightly more rapid disappearance of sore throat than occurred in those who received no treatment.

The occurrence of abnormal physical signs by day of illness in the treated and control groups is recorded in Figure 3. Following treatment with either aureomycin or penicillin there was no marked im-

provement in the physical signs. However, in almost every instance individuals receiving treatment improved somewhat more rapidly than those serving as controls. Aureomycin appeared more effective than penicillin in this regard, but the differences

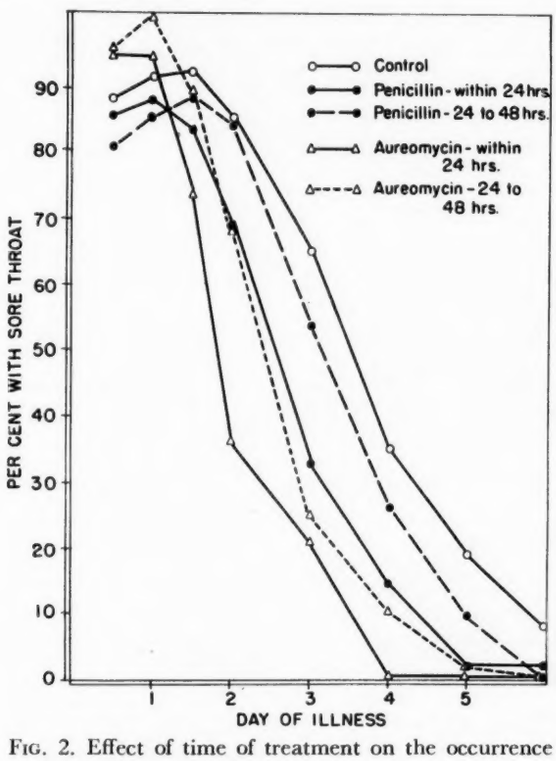


FIG. 2. Effect of time of treatment on the occurrence of the symptom, sore throat.

cannot be considered significant. Early treatment did not affect the rate of disappearance of abnormal physical signs appreciably.

Effect on Temperature. Since the course of the febrile temperature curve is related to the time of onset of the infection, the patients in the treated and control groups were divided into three categories: (1) those whose illness was of less than twenty-four hours' duration when first observed, (2) those who entered the hospital between twenty-four and forty-eight hours after the onset of illness and (3) patients whose disease began more than forty-eight hours before admission to the hospital.

Both penicillin and aureomycin altered the oral temperatures and this effect was most marked when treatment was instituted during the first twenty-four hours of illness. (Figs. 4 and 5.) In those patients who were observed within twenty-four hours of onset the number of treated patients with fever over 100°F. decreased within eight to twelve hours as compared to the control. This difference in the treated and control groups was not observed until sixteen to twenty hours after hospitalization in the patients who had been ill twenty-four to forty-eight hours. No conclusion can be made as to the effect of treatment in the group of patients observed after forty-eight hours of illness because of the small numbers involved.

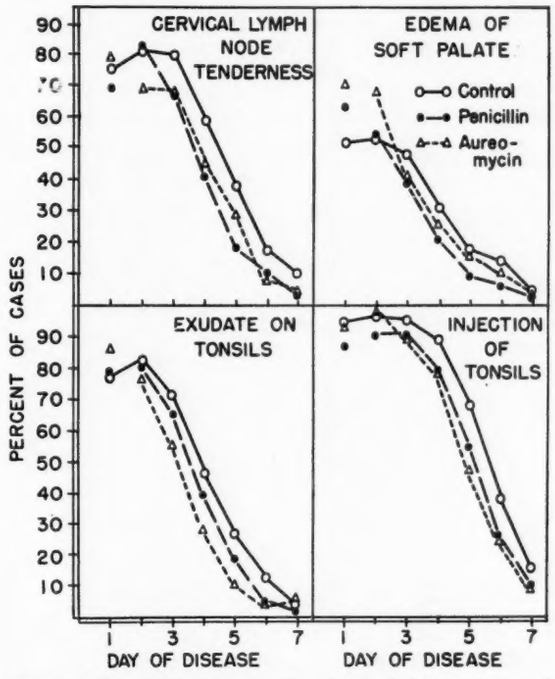


FIG. 3. Effect of therapy on the physical signs associated with streptococcal sore throat.

Aureomycin was more effective than penicillin in lowering the temperature. This result was consistent in each of the three groups but is most marked in the group which was treated during the first twenty-four hours of illness. For example, after twenty-eight hours of hospitalization 60 per cent of the control group, 30 per cent of the penicillin-treated group, and none of those receiving aureomycin had fever of over 100°F.

Effect of Treatment on Complications. Suppurative complications were unusual. There

were ten (5 per cent) patients with peritonsillar cellulitis in the control group, thirteen (6.5 per cent) in the group receiving penicillin and four (5 per cent) in the group treated with aureomycin. In two of the patients being treated with penicillin peritonsillar cellulitis developed after therapy was instituted.

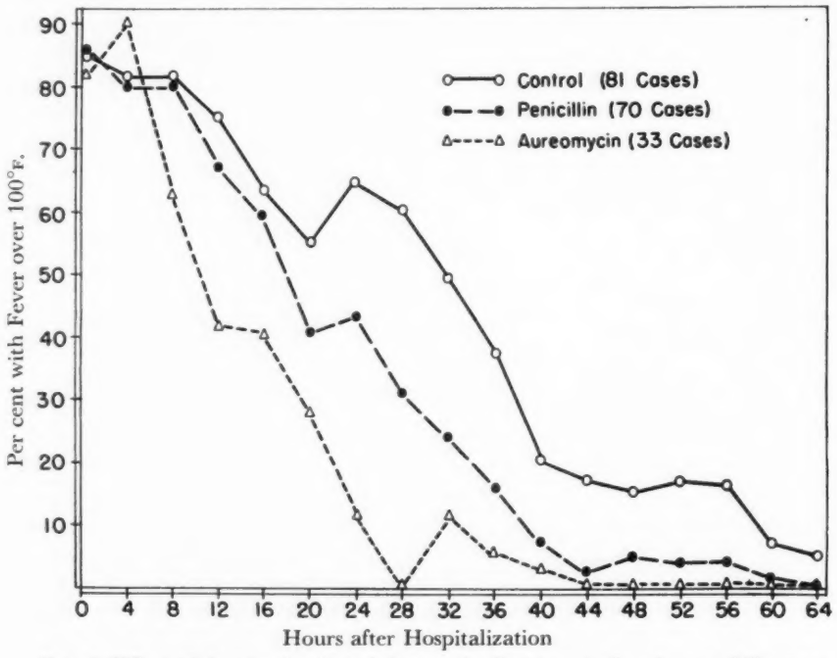


FIG. 4. Effect of therapy instituted during the first twenty-four hours of illness on the occurrence of fever.

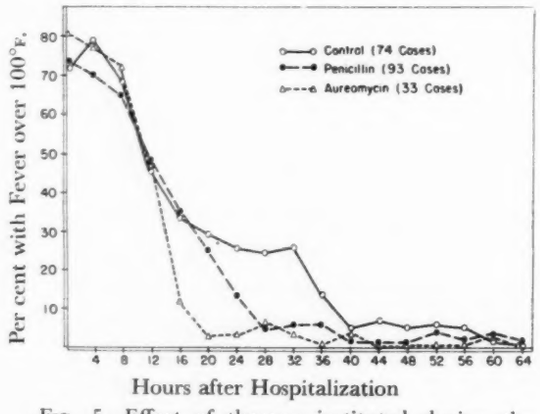


FIG. 5. Effect of therapy instituted during the second twenty-four hours of illness on the occurrence of fever.

The number of patients in whom signs of otitis media developed is not known but 6.5 per cent of the control group complained of an earache beginning twenty-four hours or more after hospitalization. This is in contrast to 2 per cent of the patients treated with penicillin and 1 per cent of the aureomycin-treated group in whom earache developed after the institution of treatment.

There were seven instances of definite acute rheumatic fever developing within ten to thirty-five days following the acute streptococcal illness. Five of these patients were in the control group which received no treatment and two developed in patients treated with penicillin. No rheumatic fever occurred in those patients treated with aureomycin. No instance of acute nephritis was observed.

LABORATORY STUDIES

Effect on Total Leukocytes. The average leukocyte count in the control group and the groups treated on the first day of illness is presented in Table II. The total count decreased more rapidly in the treated groups than in the control group. Aureomycin therapy appeared to be somewhat more effective than penicillin in its effect on the leukocyte count.

Effect of Therapy on Persistence of Group A Streptococci. The effect of therapy on group

A streptococci is shown in Figure 6. The patients included in this analysis are only those from whom group A organisms were isolated during the period of hospitalization. The most striking effect on group A streptococci was exhibited by those patients

TABLE II
EFFECT OF TREATMENT ON THE AVERAGE TOTAL LEUKOCYTE COUNT

Day of Disease	Treatment		
	None	Penicillin	Aureomycin
1	14,500	13,900	14,800
2	14,250	12,900	12,700
3	12,300	10,400	8,300
4	10,700	.....	7,500

receiving penicillin. Within one day the prevalence dropped from 98.5 to 14.1 per cent, and forty-eight hours after admission only 3.1 per cent of the individuals in this group harbored streptococci producing beta-hemolysis. Cultures obtained between three and four weeks after admission to the hospital showed that 10.7 per cent harbored the infecting type. The carrier rate for the infecting type in the control group was 46.7 per cent.

The effect of aureomycin therapy on group A streptococci in the throat differed from that observed in patients receiving penicillin. The number of isolations of streptococci did not decrease rapidly after institution of aureomycin treatment. On the second hospital day 70 per cent continued to harbor the organism but by the time of discharge from the hospital, on the fifth or sixth day, streptococci were isolated from only 4.5 per cent. In contrast to the patients receiving penicillin who showed only 10.7 per cent with the infecting type at the time of follow-up examination 44.8 per cent of the aureomycin-treated group exhibited group A streptococci of the same serologic type isolated at the time of hospitalization. New types were isolated from 23.7 per cent of the controls, 11.6 per cent of the penicillin group and 10.3 per cent of the aureomycin-treated patients. The higher incidence of new types in the control group was probably due to cross-infection in the hospital; presumably patients being treated with penicillin or aureomycin were protected from acquisition of a new organism.

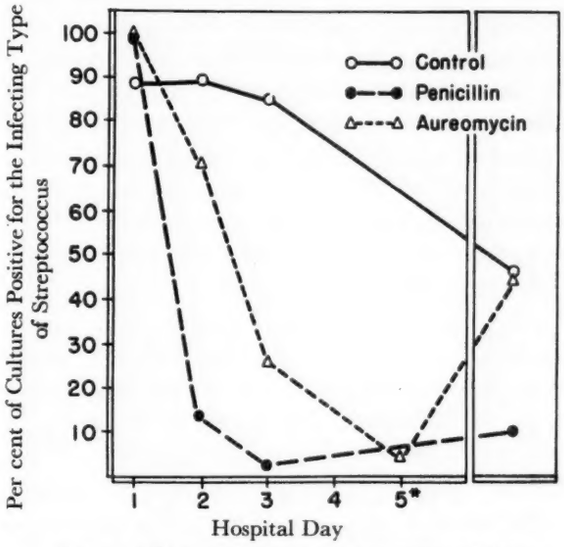


FIG. 6. Effect of therapy on persistence of the infecting type of streptococcus.

* Culture taken on fifth or sixth day.

Effect of Treatment on the Immunologic Response. Both penicillin and aureomycin therapy resulted in the inhibition of the production of antistreptolysin "O." Eighty-two per cent of the sets of sera from the control group exhibited a diagnostic increase of two or more dilution increments of the antistreptolysin titer. In contrast only 52 and 57 per cent of the patients receiving penicillin and aureomycin, respectively, showed such an increase in titer. Not only was the number of diagnostic increases in titer less in the treated groups but also the magnitude of the response was inhibited.

COMMENTS

Patients with streptococcal respiratory infections have been treated with penicillin and aureomycin but the data available are not sufficient to permit a quantitative evaluation of such therapy. The presence of an epidemic of streptococcal infections in a population group composed of young

healthy males offered an ideal opportunity for the study of various forms of treatment. In this investigation the sole criterion for inclusion in the study group was exudate on the tonsils or tissues of the oropharynx. Since previous studies[4,5] have indicated that many cases of exudative tonsillitis and pharyngitis in military populations are not related to streptococci, it was first necessary to establish the streptococcal etiology of these infections. Studies[6,7] of streptococcal epidemics have indicated that in approximately 80 to 85 per cent of individuals so infected antibodies to streptolysin "O" will develop early in convalescence. In the present study 82 per cent of the convalescent sera from the control group showed an increase in titer of antistreptolysin when compared to the titers of the acute phase sera. In addition the isolation of group A streptococci, the clinical features of the illness and the elevated leukocyte counts indicate that the majority of the infections were caused by the streptococcus.

The various features of the treated and control groups were analyzed to determine whether or not the groups were comparable. Since the absence of tonsils may affect the febrile temperature curve as well as the duration of the carrier state,[7] it is important to note that the frequency of a history of tonsillectomy was similar in the three groups. There was some variation in the frequency of certain symptoms due to a change in the infecting type of streptococcus during the course of the study. Results of previous studies[4,8] indicate that the clinical features of the illnesses may be related in part to the serologic type of group A organisms. The present observations established that type 24 streptococcus, which caused only four illnesses in the aureomycin-treated patients, was associated with a mild disease of short duration. Since type 24 was the infecting organism in many of the control group and the group which received penicillin, the effect of aureomycin would tend to be masked. Actually aureomycin proved to be even more effective than penicillin in shortening the natural course of the illness.

A favorable effect of therapy on the duration of symptoms was noted in almost every instance but it was usually not dramatic. A rather marked reduction in the frequency of sore throat was effected by both penicillin and aureomycin. This observation is interesting since sulfadiazine also is effective in this regard.[7] During the third day of illness 65, 48 and 24 per cent of the patients in the control, penicillin and aureomycin-treated groups, respectively, still complained of sore throat. The effect of early treatment on the duration of complaints was dramatic; whereas if treatment was instituted after twenty-four hours of illness, favorable results were not striking.

With the exception of nausea and vomiting the patients who received aureomycin recovered symptomatically somewhat more rapidly than those who were treated with penicillin. Although the differences were not always great, they are believed to be significant particularly since the infecting type of streptococcus in the aureomycin-treated group was associated with a more severe illness than that observed in the other two groups. The high incidence of nausea and vomiting in the group receiving aureomycin was probably due to the toxic effects of the drug.

Neither aureomycin nor penicillin therapy resulted in an appreciably beneficial effect on the abnormal physical signs. This observation is similar to that recorded in patients receiving sulfadiazine treatment.[7]

The most objective criterion available for the measurement of a favorable effect in this disease is the duration of fever. For this purpose the duration of the illness before the institution of therapy must be considered since the temperature normally drops rapidly after thirty-six to forty-eight hours of illness. Treatment during the first twenty-four hours of illness was attended by a dramatic decrease in the number of individuals with fever. This effect was most marked following aureomycin treatment.

During penicillin therapy the erythrocyte sedimentation rate returns rapidly to normal values.[9] The present study established the

fact that the leukocyte count also returns to normal and that aureomycin is more effective than penicillin in producing this effect.

Administration of aureomycin or penicillin was followed with a change in the bacterial flora of the throat. Penicillin therapy was followed with the complete and early eradication of the streptococci in most instances. In contrast to penicillin aureomycin apparently inhibited the growth of the organisms during the period of treatment but had little or no effect on the carrier state; thus its effect is similar to sulfadiazine[7] in this regard. Because of the reduced hazard of spread by the convalescent carrier the eradication of streptococci would appear to be a desirable feature of penicillin treatment.* Both drugs probably protected the individual from cross-infections in the hospital.

Since penicillin eradicates the organism rapidly and aureomycin only inhibits its growth, it is difficult to explain the fact that both compounds suppress antibody production to a similar degree. This would seem to indicate that both drugs result in the effective inhibition of the antigen (streptococci) during the period of medication. Sulfadiazine, which inhibits the growth of streptococci in the oropharynx, does inhibit antibody formation[7] although the degree of inhibition is not of the order of magnitude of that observed following aureomycin treatment.

Both compounds decreased the incidence of earaches when compared to the untreated group. The fact that acute rheumatic fever developed in only two patients receiving penicillin and five patients of the control group suggests that penicillin may prevent rheumatic fever. The two cases occurring following penicillin were the only instances observed in a much larger study of 698 patients treated with this drug and is in contrast to seventeen instances of the disease among 702 controls who received no specific therapy.[10] This study[10] established that penicillin is an effective agent in the prevention of rheumatic fever when administered during the preceding acute streptococcal infection. The fact that no case of rheumatic fever followed the acute infections treated with aureomycin suggests this drug may also prevent the subsequent development of acute rheumatic fever.

Aureomycin was more effective than penicillin in shortening the course of the acute illness. It is important to emphasize that this conclusion is justified only for the doses employed. There is some evidence that the amount of penicillin used was not optimal. Kilbourne and Loge[11] showed that when penicillin was administered in doses of 20,000 to 50,000 units every three hours antistreptolysin developed in only 14 per cent of patients. The data of Kilbourne and Loge[11] indicate that treatment with frequent injections of penicillin may eradicate the antigen (streptococci) more effectively than depot penicillin as employed in this study.

Because aureomycin therapy did not eradicate the streptococcus, it is difficult to explain its superiority over penicillin in the treatment of the acute phases of the infection. It seems entirely possible that the favorable effects observed were due to some alteration in the body metabolism as well as specific action against the invading organism.

SUMMARY

A controlled evaluation of penicillin and aureomycin therapy in 475 patients with streptococcal exudative tonsillitis and pharyngitis studied by clinical, bacteriologic and immunologic methods is reported. Aureomycin was found to be somewhat more effective than penicillin in lowering the fever and causing rapid subsidence of symptoms. Both drugs exhibited slight action on the abnormal physical signs. They were equally effective in inhibiting antibody formation. Penicillin usually eradicated the carrier state whereas aureomycin failed to influence the incidence of con-

* Subsequent studies have demonstrated that aureomycin therapy may eradicate streptococci in many instances.

valescent carriers. Earaches seldom developed in patients treated with these drugs. With either drug early treatment is required if the disease process is to be materially shortened.

Acknowledgments. The authors wish to thank Col. J. C. B. Elliott, Post Commander, Col. John K. Cullen, Surgeon, and Capt. James G. Hirsch, Chief of Medical Service, for assistance in making this study possible. Dr. E. A. Custer participated in the early phases of the investigation. The authors appreciate the technical assistance of Mary Riner, Donna Carpenter, Phyllis Guthrie, Jo Henning, Mary Margaret Hezebicks, T/Sgt. Earl C. Marple and Cpl. Joseph Page. To Dr. George F. Badger and Dr. John H. Dingle of the Department of Preventive Medicine, Western Reserve University, Cleveland, O., the authors are indebted for their active interest in this investigation.

REFERENCES

1. Maxted, W. R. Preparation of streptococcal extracts for Lancefield grouping. *Lancet*, 255: 255–256, 1948.
2. Swift, H. F., Wilson, A. T. and Lancefield, R. C. Typing group A hemolytic streptococci by M precipitin reaction in capillary pipettes. *J. Exper. Med.*, 78: 127–133, 1943.
3. Hodge, B. E. and Swift, H. F. Varying hemolytic and constant combining capacity of streptolysins: influence on testing for antistreptolysins. *J. Exper. Med.*, 58: 277–287, 1933.
4. Commission on Acute Respiratory Diseases. Endemic exudative pharyngitis and tonsillitis. Etiology and clinical characteristics. *J. A. M. A.*, 125: 1163–1169, 1944.
5. Keith, J. D. and Carpenter, J. The diagnosis of haemolytic streptococcal infection in acute nasopharyngitis. *Canad. J. Pub. Health*, 37: 127–139, 1946.
6. Rantz, L. A., Boisvert, P. J. and Spink, W. W. Etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.*, 76: 131–138, 1945.
7. Commission on Acute Respiratory Diseases. A study of a food-borne epidemic of tonsillitis and pharyngitis due to *beta*-hemolytic streptococcus, type 5. *Bull. Johns Hopkins Hosp.*, 77: 143–210, 1945.
8. Keefer, C. S., Rantz, L. A., Shuman, H. H. and Rammelkamp, C. H. Distribution of specific types of hemolytic streptococci in eight hundred and nineteen cases of infection. *Arch. Int. Med.*, 69: 952–973, 1942.
9. Jersild, T. Penicillin therapy of scarlet fever and complicating otitis. *Lancet*, 254: 671–673, 1948.
10. Denny, F. W., Wannamaker, L. W., Brink, W. R., Rammelkamp, C. H. and Custer, E. A. The prevention of rheumatic fever by treatment of the preceding streptococcic infection. *J. A. M. A.*, 143: 151–153, 1950.
11. Kilbourne, E. D. and Loge, J. P. The comparative effects of continuous and intermittent penicillin therapy on the formation of antistreptolysin in hemolytic streptococcal pharyngitis. *J. Clin. Investigation*, 27: 418–424, 1948.

Aureomycin in the Treatment of Infectious Mononucleosis*

CURTIS H. CARTER, M.D. *and* V. P. SYDENSTRICKER, M.D.
Houston, Texas *Augusta, Georgia*

AUREOMYCIN has been used in a wide variety of infectious diseases since its introduction in 1948.[1] As indicated by recent reviews on aureomycin[2,4] it appears to have a wide range of usefulness against many pathogenic microorganisms, including some of the viruses. Rose and Kneeland[2] describe their results with the use of aureomycin in infectious mononucleosis as being equivocal or negative. In a preliminary report by Lyons[3] on the use of aureomycin in three cases of infectious mononucleosis a satisfactory clinical response was obtained in each case. Spink and Yow[4] treated seven patients who had infectious mononucleosis and noted decided improvement in five of these patients within forty-eight hours. Gruskin[5] reported the use of aureomycin in one case with a significant response within twenty-four hours. Seifert et al.[6] reported on the use of aureomycin in infectious mononucleosis as compared with a placebo and concluded that aureomycin is of no value in the treatment of infectious mononucleosis. Lyons and Hard[7] reported their experiences with the use of aureomycin in eighteen cases of infectious mononucleosis as compared with twenty-five control cases and concluded that aureomycin is effective in decreasing the duration of fever, hospital stay and total course of the disease. They also believed that the duration of liver involvement was reduced with aureomycin therapy.

The purpose of this article is to report our experience with the use of aureomycin in the treatment of nine patients with infectious mononucleosis. All but one patient had a positive heterophile test and all patients presented a blood picture consistent with infectious mononucleosis. No definite dosage schedule was followed; however, in most instances the impression was obtained that an adequate course would be an initial dose of 1.0 gm. followed by 0.25 to 0.5 gm. every four to six hours for five to six days. In one case it was necessary to use aureomycin intravenously until the patient was able to swallow. No serious untoward effects secondary to the administration of the drug were noted and only two patients exhibited nausea that appeared directly related to the drug.

CASE REPORTS

CASE I. A sixteen year old white female was admitted to the ear, nose and throat service on April 22, 1949, with the chief complaints of sore throat and malaise. Onset of illness was about ten days prior to admission with the development of a sore throat. The patient was first seen by her physician on April 19, 1949, and a white exudate on both tonsils and lateral pharyngeal wall was noted. Her temperature was 100°F. and the patient was started on 300,000 units of penicillin daily. No improvement was obtained and the patient was admitted for further study.

On admission the patient appeared moderately ill and was somewhat hoarse. Moderate enlargement of cervical and submaxillary nodes was noted, and there was slight enlargement of the axillary and inguinal nodes. The nodes were non-tender. The pharynx was acutely inflamed. The tonsils were moderately enlarged and covered with a white exudate. Admission throat culture was negative for Corynebacterium

* From the Medical Service, University Hospital, Augusta, Ga., and the Medical Department, University of Georgia School of Medicine, Augusta, Ga.

diphtheriae. Routine urinalysis was negative. The white blood count was 13,700 with 37 per cent neutrophiles, 20 per cent lymphocytes, 42 per cent monocytes and 1 per cent eosinophiles. Almost all of the monocytes and lymphocytes were abnormal in appearance.

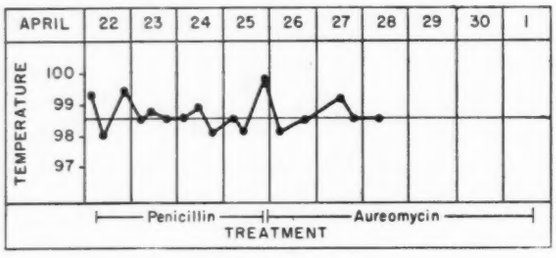


FIG. 1. Case I.

On April 24th the patient had shown little change. There was marked congestion of the scleral conjunctivas, and the palpebral conjunctivas presented a marked injection with a finely granular appearance. The pharynx showed little change except for marked hyperplasia of small lymphoid follicles on the posterior pharyngeal wall. The spleen was now palpable about 2 cm. below the left costal margin and non-tender. Repeat white blood count was 9,350 with 25 per cent neutrophiles, 61 per cent lymphocytes, 9 per cent monocytes and 5 per cent eosinophiles. Approximately 15 per cent of the lymphocytes were abnormal in that the nuclei were irregular and the cytoplasm was finely vacuolated with the basophilic material concentrated at the periphery of the cells. An occasional plasma cell was noted. Heterophile test obtained April 23rd was positive 1:448. Blood culture obtained on April 22nd was negative.

On the twenty-fifth the patient was started on 0.5 gm. of aureomycin every four hours and penicillin was discontinued. By the twenty-eighth considerable improvement had been obtained and the pharyngeal symptoms had almost subsided. The patient was dismissed to continue aureomycin for three more days. (Fig. 1.)

CASE II. A twenty-eight year old white female was admitted to the ear, nose and throat service May 1, 1949, with the chief complaints of sore throat and malaise. Two weeks prior to admission an upper respiratory infection with malaise, sore throat and enlarged cervical nodes developed in the patient. The sore throat persisted and became progressively worse. On April 29, 1949, she consulted her physician and was started on oral penicillin without improvement.

On admission the patient appeared acutely ill with a temperature of 101°F. Moderate hoarseness was evident. Anterior and posterior cervical and submaxillary nodes were moderately enlarged. There was slight enlargement of the axillary and inguinal nodes. Marked inflammation of the pharynx with a white exudate over the tonsils was noted. The white blood count was 14,500 with 30 per cent neutrophiles, 58 per cent lymphocytes and 12 per cent monocytes. About 20 per cent of the lymphocytes and monocytes were atypical. Throat culture was negative for C. diphtheriae and hemolytic streptococci. A heterophile test obtained May 2, 1949, was positive 1–896.

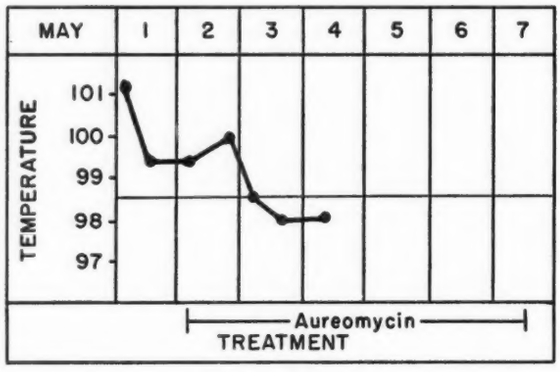


FIG. 2. Case II.

This same day the patient was given 1.5 gm. of aureomycin and then 0.5 gm. twice daily. On May 4th the patient was asymptomatic and was dismissed to continue aureomycin for two more days. (Fig. 2.)

CASE III. A twenty year old white female was admitted to the hospital on June 26, 1949, with the chief complaints of fever, chills and headache. Onset of illness was twelve hours prior to admission with headache and malaise.

The patient appeared acutely ill with a temperature of 102°F. Cervical and submaxillary nodes were enlarged. No injection of the pharynx was apparent. The spleen was not palpable. The white blood count on admission was 10,400 with 74 per cent neutrophiles, 22 per cent lymphocytes and 3 per cent monocytes. About 15 per cent of the lymphocytes were atypical. Agglutinations for typhus, typhoid, paratyphoid and undulant fever were negative. Blood culture was negative. A heterophile test obtained June 27th was positive 1–112. On the following day

the icterus index was 17 and thymol turbidity was 3.2 units.

On the twenty-seventh an initial dose of 1.5 gm. of aureomycin was given and followed by 0.5 gm. every six hours. The patient experienced moderate nausea during therapy which was partially controlled by antacids. By the afternoon of the twenty-eighth the patient had noted marked improvement. On the following day she was asymptomatic except for slight general weakness and was dismissed to continue aureomycin for three more days. (Fig. 3.)

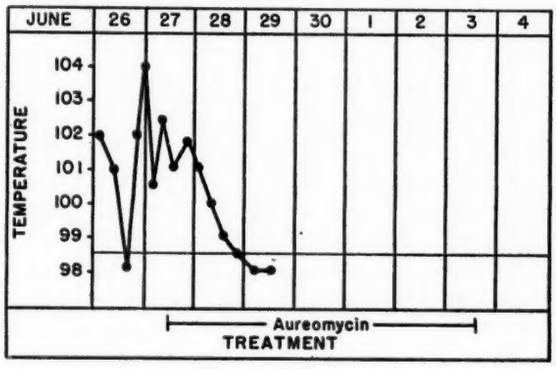


FIG. 3. Case III.

CASE IV. An eighteen year old white female was admitted to the hospital on September 29, 1949, with the chief complaints of headaches, malaise, cough, fever and sore throat. Onset of illness was one week prior to admission. On September 26th the patient consulted her physician and was given 300,000 units of penicillin. Afterwards the patient noted increasing malaise with fever and experienced a mild sore throat and slight cough.

The patient appeared acutely ill with a temperature of 103°F. The anterior and posterior cervical and submaxillary nodes were enlarged and slightly tender. Moderate pharyngitis was evident. The tonsils were moderately enlarged. The spleen was enlarged on percussion but not palpable. The white blood count on admission was 7,000 with 36 per cent neutrophiles, 62 per cent lymphocytes and 2 per cent eosinophiles. About 40 per cent of the lymphocytes were atypical. Occasional plasma cells were noted. On September 30th the heterophile test was positive 1–56. Repeat blood smears during hospitalization continued to show 70 to 80 per cent lymphocytes of which about 40 per cent were atypical. A repeat heterophile test on October 4th was 1–56. Test for cold agglutination was negative.

On admission the patient was given 1.5 gm. of aureomycin and this was followed by 0.5 gm. every six hours. The patient felt considerably improved with subsidence of sore throat by October 2nd; however, she continued to complain of moderate frontal headache and exhibited slight tenderness over the left maxillary sinus. An x-ray of the sinuses on the third of October revealed some thickening of the mucosa of the left maxillary sinus. On the fifth the patient was started on 300,000 units of penicillin daily. Aureomycin was discontinued on the sixth. The patient noted relief of headaches after three days of penicillin and was dismissed October 8th asymptomatic. (Fig. 4.)

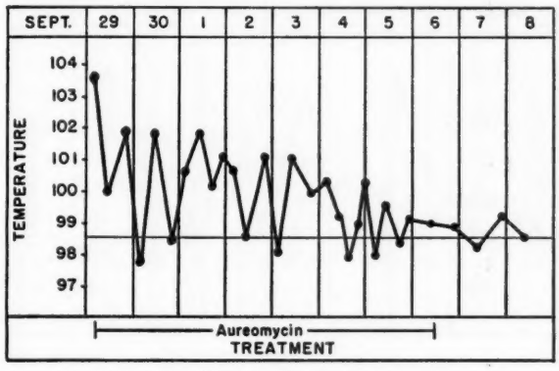


FIG. 4. Case IV.

On October 10th severe pharyngitis developed in the patient and she was readmitted. Her temperature was 101°F. Repeat examination revealed a marked follicular tonsillitis and enlarged submaxillary nodes. The patient was started on saline gargles and 300,000 units of penicillin twice daily. A repeat heterophile test was positive 1–112 on the eleventh and again on the eighteenth it was 1–224. Tests for typhus, paratyphoid, typhoid and undulant fever were negative on October 11th and 15, 1949. Repeat blood smears continued to show similar findings as noted on first admission. The patient's tonsillitis rapidly subsided and she was dismissed on the fifteenth asymptomatic.

CASE V. An eighteen year old white female was admitted to the ear, nose and throat service on November 14, 1949 with the chief complaints of sore throat, malaise and fever. Onset of illness was two weeks prior to admission when in the patient conjunctivitis developed with edema of the lids which gradually subsided over a period of a few days. On the seventh the patient had noted onset of sore throat and fever. The following day she was started on penicillin; however,

the sore throat increased in severity and by the tenth swallowing had become very difficult. On this date increasing cervical adenopathy was noted and the patient was also started on "sulfa" drug. Therapy was continued but no improvement was obtained.

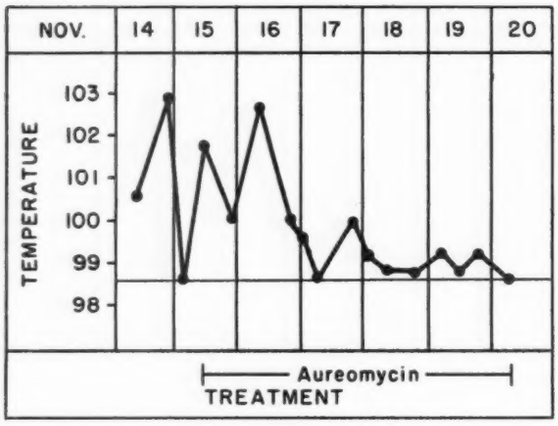


FIG. 5. Case v.

On admission the patient appeared acutely ill with a temperature of 100.4°F. Marked edema of the eyelids was noted with injection of palpebral conjunctivas which presented a granular appearance. The parotid glands were enlarged and tender and the pharynx was markedly edematous and injected, with ulceration of the tonsils. There was marked enlargement of the cervical and postauricular nodes with moderate enlargement of the axillary and inguinal nodes. All nodes were moderately tender. The spleen was palpable 3 cm. below the left costal margin. The white blood count was 10,000 on admission with 34 per cent neutrophiles, 60 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophiles. About 30 per cent of the lymphocytes were atypical. Throat culture revealed diphtheria-like organisms and a few hemolytic streptococci. The heterophile test on November 16th was positive 1–896.

On November 15th the patient was given 200 mg. of aureomycin intravenously and two hours later was able to eat with very little discomfort. This dosage was repeated four hours after the first injection and thereafter 250 mg. were given every four hours by mouth. On the sixteenth the patient felt markedly improved, but on the following day she noted a return of sore throat and aureomycin was again administered intravenously for two doses eight hours apart. Pharyngeal symptoms subsided and afterwards oral therapy was resumed with rapid improvement.

The patient was dismissed on November 20th asymptomatic. Only slight lymphadenopathy was evident and the spleen was barely palpable. (Fig. 5.)

CASE VI. A thirteen year old white female was admitted to the hospital on December 25, 1949, with the chief complaints of headache, fever, nausea and vomiting, and general malaise. Onset of illness was December 21, 1949, when the patient experienced a severe chill followed by frontal headache. On that date her temperature was 105°F. and the patient obtained some relief with aspirin. Afterward she had nausea and vomiting and was later seen in the emergency room of the hospital. At that time an x-ray of the chest was negative and the white blood count was 2,000 with 70 per cent neutrophiles and 30 per cent lymphocytes. Most of the lymphocytes were atypical. The family did not desire hospitalization at that time; however, the next day the patient's symptoms became worse and she was returned to the hospital for admission.

The patient appeared acutely ill with a temperature of 104°F. A maculopapular, erythematous eruption was noted over the face and upper trunk. Increased lacrimation was evident. There was moderate injection of the pharynx with evident lymphoid follicles on the posterior pharynx. The anterior and posterior cervical nodes were moderately enlarged and tender. Slight enlargement of axillary and inguinal nodes was noted. The spleen was palpable at the left costal margin. There was slight nuchal rigidity. A spinal puncture was performed and examination of the fluid was negative. Throat culture revealed a non-hemolytic streptococcus. Blood culture was negative. The heterophile test on December 28th was 1–56 and a cold agglutination test was negative.

On admission the patient was given 0.5 gm. of aureomycin and then 250 mg. every four hours. During the first twenty-four hours of therapy the patient had nausea and vomiting which subsided with continuation of therapy. By the twenty-eighth the patient was asymptomatic except for some general weakness. During a temperature spike on the twenty-ninth the patient experienced mild malaise. Therapy was continued until January 1, 1950, and the patient was dismissed entirely asymptomatic. A heterophile test obtained on January 3rd was positive 1–112. (Fig. 6.)

A repeat white blood count on the fourteenth was 5,100 with 30 per cent neutrophiles, 64 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinphiles; 50 per cent of the lymphocytes were atypical. A repeat heterophile test on this date was 1–56. On this date the patient was

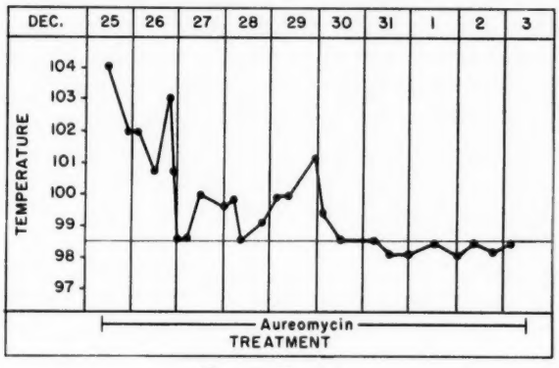


FIG. 6. Case VI.

symptom-free and examination revealed only slight cervical adenopathy.

CASE VII. A twenty-one year old white female was admitted to the hospital surgical service on October 31, 1949, with the chief complaint of pain in right lower abdomen. Onset of illness was October 30th with pain in the right lower abdomen not associated with nausea. The severity of the pain increased progressively with fluctuations in intensity.

Examination on admission revealed moderate injection of the pharynx and some enlargement of cervical lymph nodes. Moderate muscle spasm was noted over the right lower quadrant with tenderness most marked below and lateral to McBurney's point. Marked rebound tenderness was present. White blood count was 5,650 with 64 per cent neutrophiles and 36 per cent lymphocytes. Two repeat counts made later the same day were 8,800 and 6,300. A few atypical lymphocytes were noted and the possibility of infectious mononucleosis with mesenteric lymphadenitis was considered; however, during twenty-four hours of observation the right lower quadrant pain increased and an appendectomy was performed on November 1st. Pathologic examination of the appendix revealed acute non-suppurative appendicitis with slight inflammatory cell infiltrate of the coats.

From the date of admission until November 3rd the patient received 300,000 units of penicillin daily. On the day of the operation the patient's temperature began to climb and the patient complained of marked general malaise. Repeat blood smears revealed numerous atypical lymphocytes consistent with infectious mononucleosis. On the third of November the patient was started on 0.25 gm. aureomycin every six hours. Within forty-eight hours the patient stated that all malaise had subsided; however,

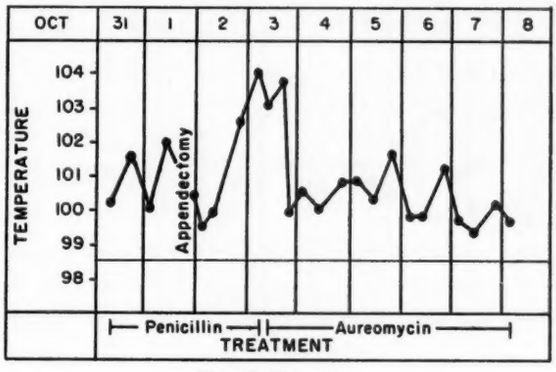


FIG. 7. Case VII.

she continued to have some temperature elevations until November 8th when she was dismissed to continue convalescence at home. (Fig. 7.)

CASE VIII. A thirty year old white female was admitted to the hospital July 29, 1949, with the chief complaints of cough, nausea and vomiting, and severe headache. Onset of illness was about four weeks prior to admission with cough and coryza. Two weeks later the cough became productive and she began to feel feverish. At this time she received one dose of penicillin and took "sulfa drug" for three days without improvement. Six days prior to admission she experienced a chill and because of fever and malaise went to bed. At this time she received another dose of penicillin and another four days prior to admission.

The patient appeared acutely ill. The pharynx was moderately injected and tender; enlarged anterior and posterior cervical nodes were present. Bronchial breath sounds and medium moist rales were noted over the right hilar area posteriorly. X-ray of chest revealed slightly increased bronchovascular markings in right lower lobe region. On July 30th examination of a stained blood smear revealed a moderate number of large lymphocytes, many of which were atypical and consistent with infectious mononucleosis. On the same day agglutinations for typhus, typhoid, paratyphoid and undulant fever were negative. The test for cold agglutinins was negative and the heterophile test on August

1st was positive 1–224. A blood culture obtained on admission was negative.

On July 29th the patient was given 1.5 gm. aureomycin and then 0.5 gm. every six hours. By July 31st there was almost complete disappearance of all symptoms. A repeat x-ray on

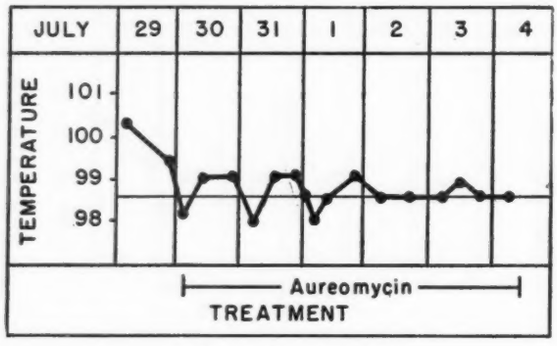


FIG. 8. Case VIII.

August 1st was reported negative. The patient was dismissed on the fourth entirely asymptomatic. (Fig. 8.)

CASE IX. A white male twenty-three years of age was admitted to the hospital January 21, 1950, with the chief complaints of nausea and vomiting and generalized abdominal discomfort. Present illness began about December 31, 1949, with pharyngitis and fever which improved with penicillin therapy; however, the patient continued to experience general malaise and he noted onset of anorexia, nausea and return of sore throat one week before admission. Nausea with vomiting began three days before admission and for thirty-six hours prior to admission the patient was unable to retain anything by mouth.

In 1948 a diagnosis of bronchiectasis, minimal, right lower lobe had been made elsewhere.

Examination on admission revealed a poorly nourished patient with slight icterus of skin and scleras. His temperature was 99°F. The pharynx was injected, with hypertrophy of lymph follicles. The anterior and posterior cervical, submental and axillary nodes were enlarged and tender. There was moderate epigastric tenderness. The spleen was palpable at the left costal margin and liver palpable 3 cm. below right costal margin. The white blood count was 15,200 with 26 per cent neutrophiles and 74 per cent lymphocytes. About 25 per cent of the lymphocytes were atypical with many irritation forms. The serum amylase was normal on two occasions. The heterophile test on January 23, 1950, was positive 1:448 and on this date the icterus index was 14.6, van den Bergh 1.6 (indirect), and a thymol turbidity test showed 13 units. The urine was positive for excess urobilinogen and positive for bile. On the twenty-fifth, three days after starting therapy, urine urobilinogen was normal and the urine was only faintly positive for bile. On the twenty-sixth the cephalin flocculation was 4+, the icterus index was 11.5 and the van den Bergh was 0.67. The thymol turbidity was 14.4 units.

For the first twenty-four hours the patient was given symptomatic therapy and intravenous fluids. On January 22nd intravenous aureomycin, 100 mg. every four hours, was started. Within thirty-six hours the patient was improved sufficiently to take fluids and medication by mouth and aureomycin, 250 mg. orally every six hours, was started and continued until his dismissal on January 26, 1950.

Rapid subjective improvement was noted in this case following institution of aureomycin therapy and symptoms referable to the complicating hepatitis declined promptly.

COMMENTS

In evaluating therapy in infectious mononucleosis it is well to keep in mind the protean manifestations and extremely variable course of the disease.[8] For this reason and in view of the fact that a specific etiologic agent has not been identified it is realized that considerable caution should be exercised in appraisal of results.

In the case reports presented the beneficial effect of aureomycin was impressive in each instance. All of the patients but one exhibited pharyngeal involvement and each of these showed rapid and marked improvement following institution of aureomycin therapy. The improvement of the severe angina in Case V following intravenous aureomycin therapy was dramatic and most impressive. Of interest was the occurrence of a severe follicular tonsillitis in Case IV, two days after dismissal, which responded promptly to penicillin; prior to the first admission, penicillin was without benefit. General malaise, noted by each patient, subsided rapidly and each experienced a sense of well-being within twenty-four to seventy-two hours after institution of therapy with aureomycin. As

noted in the temperature charts, the response of the fever was variable; however, Case IV was complicated by maxillary sinusitis and therapy in Case VII was started soon after an appendectomy. Although Cases I and II were acutely ill, the febrile reaction was slight in each case.

Essentially similar beneficial effects were noted in the patients reported regardless of whether the therapy was started soon or late after the onset of the illness. However, the possibility of coincidental improvement following institution of therapy in some of the cases has to be considered. When taken together with the satisfactory responses already reported,[3–5] it would appear that aureomycin seems to be beneficial in the treatment of infectious mononucleosis and is certainly worthy of further clinical trial in this disease.

In Case IV the heterophile test was negative prior to therapy with aureomycin and became positive 1–112 five days after discontinuing treatment and later the titer was 1–224. In Case VI a similar finding was noted. Although not conclusive, this would suggest that therapy with aureomycin has no effect on the development of a positive heterophile test. Also, therapy with aureomycin did not appear to influence the blood picture during the course of the disease in the case reports described before.

SUMMARY

The results obtained with aureomycin in the treatment of nine patients with infectious mononucleosis are presented.

In each instance a beneficial effect was obtained. One patient with severe angina responded dramatically to aureomycin administered intravenously.

It is believed that these results, in addition to those already reported, warrant further clinical trial of aureomycin in the treatment of infectious mononucleosis.

REFERENCES

1. Duggar, B. M. Aureomycin: a product of the continuing search for antibiotics. *Ann. New York Acad. Sc.*, 51: 177, 1948.
2. Rose, H. M. and Kneeland, Y. Jr. Aureomycin in the treatment of infectious diseases. *Am. J. Med.*, 7: 532, 1949.
3. Lyons, H. A. Aureomycin in the treatment of infectious mononucleosis. *U. S. Nav. M. Bull.*, 49: 1,076, 1949.
4. Spink, W. W. and Yow, E. M. Aureomycin: present status in the treatment of human infections. *J. A. M. A.*, 141: 964, 1949.
5. Gruskin, B. J. Aureomycin in acute infectious mononucleosis. *Ann. Int. Med.*, 31: 678, 1949.
6. Seifert, M. H., Chandler, V. L. and Winkle, W. V. Aureomycin in infectious mononucleosis. *J. A. M. A.*, 142: 1,133, 1950.
7. Lyons, H. A. and Hard, E. M. The effect of aureomycin therapy in infectious mononucleosis. *Bull. New York Acad. Med.*, 26: 279, 1950.
8. Custer, R. P. and Smith, E. B. The pathology of infectious mononucleosis. *Blood*, 3: 831, 1948.

Incidence of Lipoid Pneumonia in a Survey of 389 Chronically Ill Patients*

B. W. Volk, M.D., L. Nathanson, M.D., S. Losner, M.D., W. R. Slade, M.D. *and* M. Jacobi, M.D.

Brooklyn, New York

In a recent publication the authors[1] reported a simple method for the diagnosis of lipoid pneumonia by the microscopic examination of the sputum in patients whose history, physical examination and roentgenographic findings were suggestive of lipoid pneumonia. These results encouraged us to survey with this method a large number of chronically ill patients to determine the incidence of previously undetected cases of lipoid pneumonia.

The importance of aspirated oil in the production of pulmonary lesions has long been recognized. Guiesse-Pellissier[2] in 1920 observed the effect of injection of olive oil into the lungs of dogs and rabbits. He noted phagocytosis of the oily drops by large monocytes in the absence of inflammation in the lung. In subsequent experiments[3] intratracheal instillation of other oils such as chaulmoogra oil and liquid petrolatum showed a similar picture, then called "proliferative bronchopneumonia." Laughlin[4] was the first to describe the pulmonary lesions following aspiration of oil in the human. The histologic differences in the lesions produced by the aspiration of animal, vegetable and mineral oil were extensively studied by Pinkerton.[5] He showed that neutral vegetable oils were practically innocuous while some of the animal oils cause marked tissue reaction characterized by proliferation of macrophages and giant cells.

In the following years an increasing number of cases of oil aspiration pneumonia was reported.[6–9] In 1943 Sweeney[10] collected 264 cases of lipoid pneumonia from the literature, 131 of which were caused by the ingestion of mineral oil. Lipoid pneumonia, first thought to occur only with chronic or disabling ailments, has also been observed in apparently healthy individuals.[11] More recent reports[12,13] indicate that the introduction of oils into the nose and throat in pure form or as a vehicle for other medication produces chronic pulmonary lesions more frequently than had generally been assumed.

The great variation in the clinical picture of this disease in adults makes the differential diagnosis of lipoid pneumonia difficult, particularly because the roentgenographic findings are frequently atypical and inconclusive. Thus Freiman[14] reported about half of the autopsied cases of lipoid pneumonia to be incidental findings and clinically asymptomatic. In an analysis of the symptoms of lipoid pneumonia Sodeman and Stuart[15] emphasized the large number of asymptomatic cases and stressed the numerous other pulmonary conditions which may be associated with lipoid pneumonia.

Roentgenologic examination frequently presents the picture of low grade pulmonary infection.[16–19] At times the differential diagnosis of lipoid pneumonia and bronchogenic carcinoma may be difficult or impossible from the roentgenograms.

MATERIAL AND METHOD

A twenty-four hour collection of sputum was obtained daily for three to five days from 389 chronically ill patients. These patients had been

* From the Departments of Pathology, Medicine and Roentgenology, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y.

TABLE 1

DATA ON FIFTY-SEVEN PATIENTS WITH LIPOID PNEUMONIA

Patient	Age	Sex	Clinical Diagnosis	History of Intake of*	Symptoms	Physical Findings	Evidence of Lipoid Pneumonia by		
							Sputum	Lung Aspiration	Roentgenograms†
1.	79	M	Parkinson's disease	(1)	Cough	Moist bubbling rales, both lower lobes	+	+	++++
2.	56	F	Parkinson's disease	(2)	Productive cough	.....	+	+	++++
3.	63	F	Parkinson's disease	(1)	.....	.....	+	+	++
4.	62	M	Parkinson's disease	(1,2)	Cough	.....	+	+	++
5.	54	M	Parkinson's disease	(4)	.....	Moist rales, right lower lobe	+	+	−
6.	59	F	Parkinson's disease	(1)	.....	.....	+	+	+
7.	52	M	Parkinson's disease	(1,3)	Cough	.....	+	+	+
8.	51	M	Parkinson's disease	(1)	.....	.....	+	+	++
9.	54	M	Parkinson's disease	(1)	.....	.....	+	+	−
10.	78	M	Parkinson's disease	(1,2)	Productive cough	Fine and coarse moist rales, right lower lobe	+	+	++++
11.	52	F	Parkinson's disease	(1)	.....	.....	+	+	++++
12.	72	F	Parkinson's disease	(1)	Cough	Coarse rales, right lower lobe	+	+	++++
13.	51	F	Parkinson's disease	Denied	.....	.....	+	+	+
14.	66	F	Parkinson's disease	(1)	.....	.....	+	+	−
15.	43	F	Parkinson's disease	(1)	.....	.....	+	+	++++
16.	51	M	Multiple sclerosis	Denied	.....	.....	+	+	+
17.	53	M	Multiple sclerosis	(2)	.....	.....	+	+	+
18.	40	M	Multiple sclerosis	(4)	Productive cough	Moist rales, both lower lobes	+	+	+
19.	47	F	Multiple sclerosis	(1)	.....	.....	+	+	++
20.	38	M	Multiple sclerosis	(1)	Cough	.....	−	+	++++
21.	15	F	Cerebral palsy	(1)	.....	.....	+	+	++
22.	59	F	Cerebral palsy	(1)	.....	.....	+	+	++++
23.	30	M	Cerebral palsy	(1)	.....	.....	−	+	++++
24.	36	M	Cerebral palsy	(1)	Productive cough	.....	+	+	++
25.	43	F	Cerebral palsy	(4)	.....	Fine moist rales, right lower lobe	+	+	+
26.	31	F	Cerebral palsy	(1,2)	.....	.....	+	+	++++
27.	60	F	Hemiplegia	(1)	Expectoration	Coarse rales and wheezing, right lower lobe	+	+	−
28.	74	M	Hemiplegia	(4)	Productive cough	Fine moist rales, both lower lobes	+	+	++++
29.	82	M	Hemiplegia	(1)	Productive cough	Wheezing and fine moist rales, both lower lobes	+	+	++++
30.	73	F	Hemiplegia	(1)	Cough	Coarse rales, both lower lobes	+	+	++++
31.	56	F	Amyotrophic lateral sclerosis	(1)	.....	.....	+	+	−
32.	59	F	Degenerative disease of central nervous system	(1)	Cough	.....	+	+	++
33.	39	M	Progressive muscular dystrophy	(1 2)	.....	.....	+	+	++++
34.	66	M	Rheumatoid arthritis	(1,2)	Productive cough	Moist rales, left lower lobe	+	+	++++
35.	65	M	Rheumatoid arthritis	(2)	Productive cough	Moist bubbling rales, both lower lobes	+	+	++
36.	60	F	Rheumatoid arthritis	(1,2)	Productive cough	Moist rales, both lower lobes	+	+	−
37.	70	F	Rheumatoid arthritis	Denied	Productive cough	.....	+	+	++++
38.	65	F	Rheumatoid arthritis	(1)	Productive cough	Dullness and few moist rales, right lower lobe	+	+	++++
39.	79	M	Rheumatoid arthritis	(2)	.....	.....	+	+	+
40.	68	F	Rheumatoid arthritis	(1)	Produtive cough	.....	+	+	++
41.	70	M	Hypertrophic arthritis	(2)	.....	.....	+	+	+
42.	72	F	Hypertrophic arthritis	(1)	.....	.....	+	+	+
43.	67	M	Arteriosclerotic heart disease	(1)	.....	.....	+	+	+
44.	76	M	Arteriosclerotic heart disease	(1,2)	Productive cough	Increased breath sounds	+	+	++++
45.	69	M	Arteriosclerotic heart disease	(1,2)	Productive cough	Bronchial breathing, both lower lobes	+	+	++
46.	84	F	Hypertensive cardiovascular disease	1,2,3)	.....	.....	+	+	+
47.	87	M	Hypertensive cardiovascular disease	(1,2)	Productive cough	Fine moist rales, right lower lobe	+	+	++++
48.	59	M	Hypertensive cardiovascular disease	(1,2,3)	Productive cough	Fine moist rales, right lower lobe	+	+	+
49.	64	F	Generalized arteriosclerosis	(1)	.....	.....	+	+	++
50.	84	M	Generalized arteriosclerosis	(1)	Productive cough	Moist fine rales, right lower lobe	+	+	++++

* (1) mineral oil; (2) nose drops; (3) other oil-containing medication; (4) history not elicited

† Symbols:

++++ Characteristic for lipoid pneumonia
++ Consistent with lipoid pneumonia
\+ Uncharacteristic pulmonary findings
− Lungs negative

TABLE I (*Continued*)

Patient	Age	Sex	Clinical Diagnosis	History of Intake of*	Symptoms	Physical Findings	Evidence of Lipoid Pneumonia by		
							Sputum	Lung Aspiration	Roentgenograms†
51.	64	M	Bronchiectasis	(1,2)	Productive cough	Moist fine rales, right lower lobe	+	+	++
52.	65	F	Bronchial asthma	(1)	Cough	Wheezing and moist coarse rales, both lower lobes	+	+	+
53.	53	F	Diabetes mellitus, general arteriosclerosis	(1)	.....	.....	+	no biopsy	+
54.	68	F	Diabetes mellitus	(1)	Cough	.....	+	+	+
55.	60	F	Carcinoma of cervix	(1)	.....	.....	+	+	+
56.	80	M	Carcinoma of rectum, senile dementia	(1)	.....	.....	+	+	++
57.	77	M	Carcinoma of gallbladder	(1)	.....	.....	+	+	+

See explanation for footnotes on page 317.

placed on a strictly fat-free diet beginning four days prior to this examination and this diet was continued throughout the period of sputum collection. A drop of sputum was deposited on each of four glass slides with a platinum loop and a drop of saline was added to establish a thin spread. If the sputum was thin and watery, the specimen was centrifuged for five minutes, the sediment then being spread on a glass slide in a similar manner. The slides were dried in the incubator. Two slides were stained with Sudan IV, as previously described,[1] and two with Wright's stain as modified by Lillie.[20] The sputum was considered positive for lipoid pneumonia when the Wright stain showed the characteristic macrophages containing clusters of vacuoles and if these stained orange-brown in Sudan IV or if abundant extracellular fat-staining material was present.

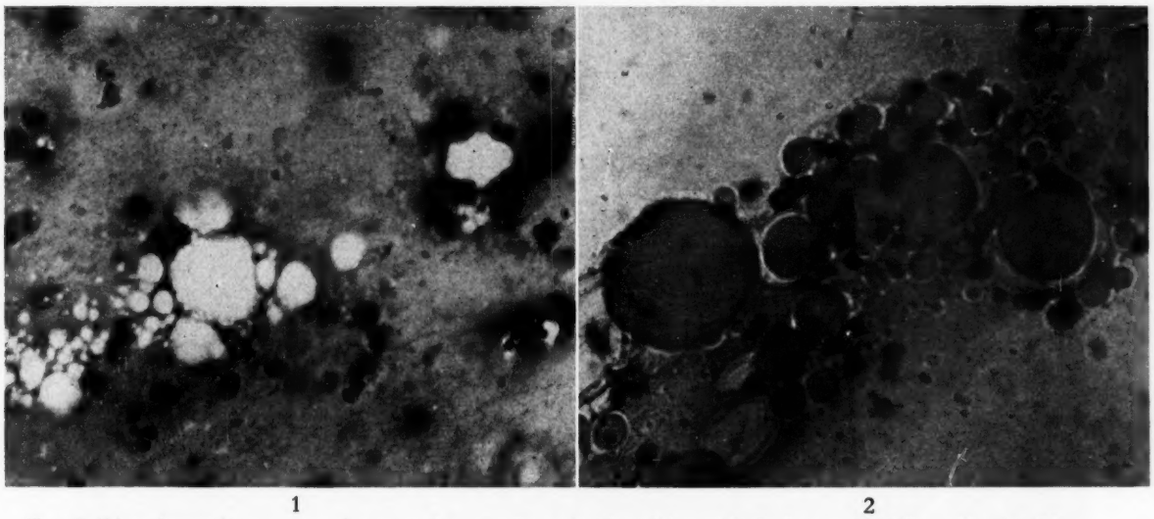
In fifty-four patients whose sputum contained lipophages or large amounts of free lipoid an aspiration from the lungs was performed. The aspirated material was spread thinly on several glass slides, fixed through the flame and stained in a manner similar to that used for the sputa. All patients had roentgenographic studies of the chest. When indicated, repeat roentgenograms were taken before and after examination of the sputa and of the material aspirated from the lung.

RESULTS

Of 389 patients examined, fifty-seven (14.6 per cent) were found to have lipoid pneumonia diagnosed by at least two of the methods of identification used. (Table I.) Forty-nine patients showed typical lipophages in the sputum. (Figs. 1 and 2.) In six patients only few lipoid-containing macrophages were observed. However, abundant amounts of Sudan-positive material in single, small or large droplets or arranged in clusters were found. This picture must also be considered indicative of lipoid pneumonia because the large drops are assumed to result from confluence of intracellular lipoid material set free after disintegration of the macrophages. In one patient from whom the sputum could not be obtained because of cerebral palsy and inability to expectorate, the diagnosis was made by lung aspiration and roentgenographic findings. In a second the sputum was continuously negative although the aspiration and roentgenographic findings were positive.

In fifty-four patients of this series the findings were confirmed by aspiration of material from the lung which was classified as positive only when macrophages containing the typical intracellular clusters of lipoid droplets were found and when these were identified with the Sudan IV stain. (Fig. 3.) One patient refused to submit to this procedure. In seven patients aspiration from the lung had to be repeated because the material obtained at the first attempt did not yield lipoid-containing macrophages.

During the time of this study eight of the fifty-seven patients with a clinical diagnosis of lipoid pneumonia died. Five of these



1 2

FIG. 1. Lipophages in sputum; the vacuoles may be stained positive with Sudan IV–Wright stain. × 450.
FIG. 2. Cluster of lipoid-containing macrophages as well as several free lipoid droplets, Sudan IV stain. × 500.

were autopsied and all were found to have this condition.

CLINICAL DATA

The majority of the patients of this group had diseases of the central nervous system. (Table I.) The rest were admitted because of rheumatoid arthritis, arteriosclerosis, hypertensive heart disease and progressive muscular dystrophy. None of them had received mineral oil during their stay in the hospital. However, from the history it was elicited that fifty (87.7 per cent) had previously taken mineral oil, nose drops or oil-containing medication over a period varying from a few weeks to several years. Seven (12.3 per cent) patients denied the intake of drugs in any form. However, several were in poor mental condition so that the information was considered unreliable. Forty (70.2 per cent) patients were bedridden or confined to a wheelchair. Twenty (35.1 per cent) patients had fine or coarse moist rales over the right or less frequently over both lower lobes upon physical examination. In twenty-seven (47.3 per cent) patients a history of intermittent productive cough was elicited. Three patients presented a picture of bronchiectasis characterized by expectoration of copious amounts of sputum, low grade fever, cough and signs and symptoms of chronic bronchitis. Bronchoscopy was performed in four patients after the sputum examination and aspiration of material from the lung. There were very few patients who had difficulty in swallowing and these had degenerative diseases of the central nervous system.

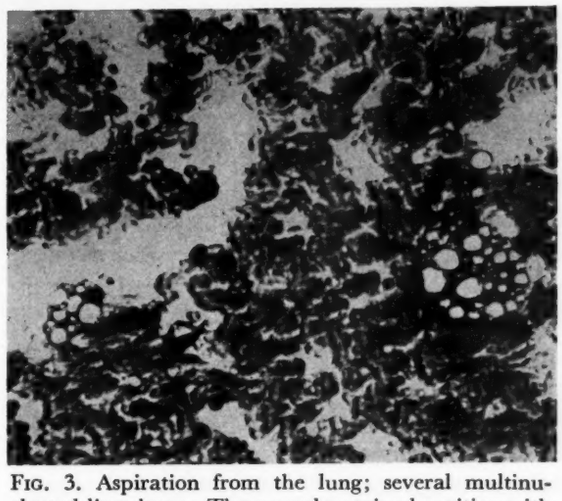
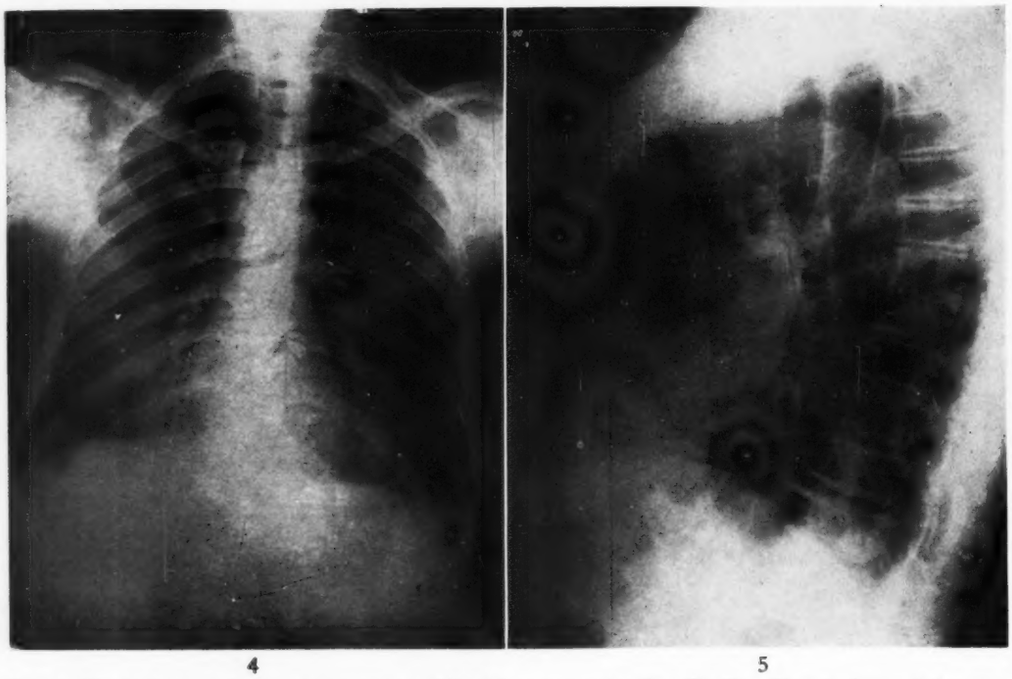


FIG. 3. Aspiration from the lung; several multinucleated lipophages. The vacuoles stained positive with Sudan IV–Wright stain. × 300.

While the preceding analysis presents statistically the symptoms shown by the patients one fact should be stressed. It was rather striking that several of the patients in whom lipoid pneumonia was found had frequent bouts of acute pneumonitis. They were accompanied with sudden elevations of temperature up to 105°F., considerable cough with little or no sputum, moderate



4 5

FIG. 4. Typical ground glass appearance of lipoid pneumonia; fine fibrillar fibrosis, lower lobes predominantly involved.

FIG. 5. Segmental retrocardiac infiltration demonstrated from lateral view; postero-anterior study essentially negative.

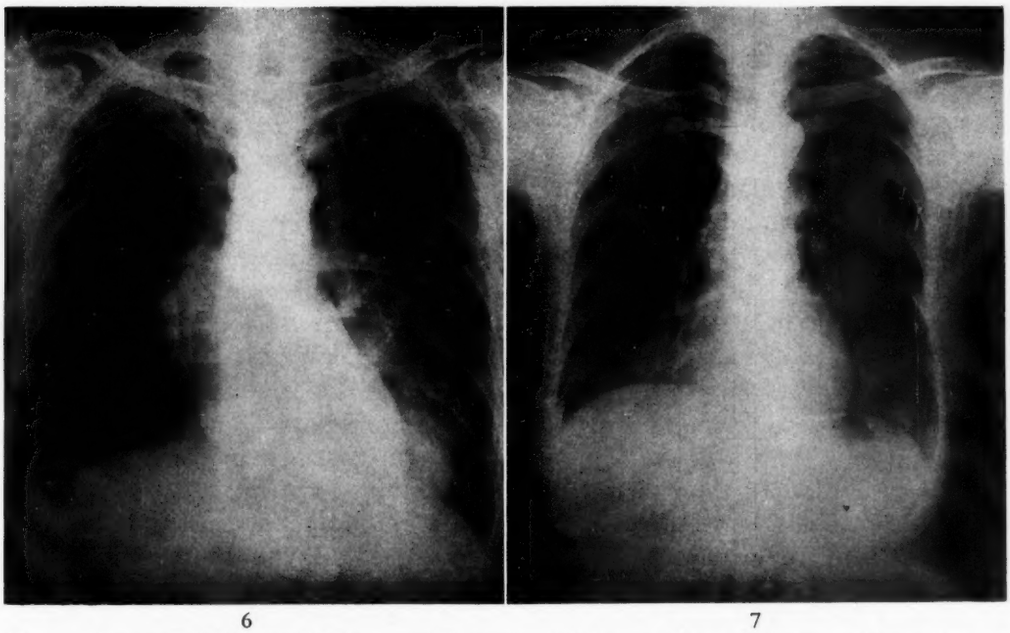
prostration, little or no cyanosis but marked tachypnea. Blood counts generally revealed a moderate leukocytosis with little or no polynucleosis. These bouts, frequently occurring two or three times a year in the same patient, generally subsided quite rapidly under chemotherapy within two or three days.

ROENTGENOGRAPHIC FINDINGS

In twenty patients the roentgenographic studies of the chest were considered characteristic of lipoid pneumonia. (Fig. 4.) The sputum was consistently negative in one of these patients although a positive aspiration was obtained yielding typical macrophages. Another patient refused to cooperate and no sputum was obtained. Here again aspiration yielded the characteristic findings.

The roentgenograms of the remaining thirty-seven patients were not sufficiently characteristic from our routine postero-anterior studies to justify a diagnosis of lipoid pneumonia. Following the finding of either a positive sputum, aspiration biopsy or both, we restudied these patients with lateral, oblique and, when indicated, overexposed film examinations, and in thirty-one of these patients we gained the impression that there was considerable retrocardiac and peribronchial infiltration present. In thirteen of the latter group the retrocardiac changes were sufficiently pronounced with distinct peribronchial and segmental infiltration to consider the probability of an aspiration pneumonia involving the most dependent portions of the lung fields consistent with lipoid pneumonitis. (Fig. 5.) Eighteen of these patients showed considerable peribronchial exaggeration and parenchymal fibrosis of both lungs which one could not consider radiographically positive for lipoid pneumonia. These findings, however, may indicate early or late changes of this disease. In six patients in whom the roentgenograms were considered negative a positive sputum and positive aspiration was obtained.

Ten of the original twenty patients with studies characteristic of or consistent with lipoid pneumonia first came to our attention with an extensive bilateral basal infiltration



6 7

FIG. 6. Circumscribed consolidation, mesial portion left lower lobe, simulating malignancy; adenopathy of both hilar regions; fibrosis of both lungs.
FIG. 7. Circumscribed opacity, right base; lateral view shows lesion within middle lobe. The picture simulates a neoplasm.

of varying extent and density. The right lower lobe and particularly the medial and cardiodiaphragmatic segment of the right lower lobe was the most frequent single lobe involvement. An isolated left lower lobe lesion was present in four instances. Middle lobe involvement was present in several instances in addition to the right lower lobe. The right middle lobe was at times more extensively involved than the right lower lobe. Upper lobe infiltration occurred only in widespread lesions. Isolated upper lobe abnormalities such as one observes with acute lipoid pneumonitis in infants were not present in our series.[21]

We have observed these patients for intervals ranging from one to ten years. Frequently the lesions changed very little from the original roentgenograms. In four instances in which we were able to follow the lesion from its inception, the involvement progressed from a peribronchial to a more generalized patchy, irregular, coalescent lobular and lobar lesion. The density varied considerably terminating frequently in a ground glass lesion or in a dense homogeneous consolidation. Nodular and fibrotic densities were present and were best demonstrated by overexposed films and Bucky diaphragm studies. The lesions and surrounding parenchymal structures at times retracted and became more localized. In five instances a sharply circumscribed and dense lesion developed resembling a neoplasm of the lung. (Figs. 6 and 7.) These lesions are frequently the end stage of a lipoid pneumonia. Overexposed films may help in differentiating them from a neoplasm by demonstrating linear and nodular fibrosis within the lesion.

A bronchographic study was done in four instances to help differentiate the lesion from bronchiectasis and "bronchial" neoplasm. We have observed a dead tree effect with cut off obstructed bronchioles and poorly draining alveoli. In two instances the bronchi skirted and were displaced by the lesions or showed evidence of retraction and crowding as a result of fibrosis and atelectasis. We have not observed evidence of cylindrical or saccular bronchiectasis, lung abscess or lung necrotization. Thickened pleura and chronic emphysema are frequent findings. We have not demon-

strated pleural effusion. A localized pneumothorax occurred only in two instances following aspiration. This complication of aspiration is rare due to the obliterative pleuritis that is frequently present. It produces no ill effects and the air is rapidly absorbed.

COMMENTS

In this survey of 389 chronically ill patients fifty-seven (14.6 per cent) cases of lipoid pneumonia were encountered. A good many patients were partially or completely immobilized. Most of them used mineral oil as a laxative. Others had used nose drops or various oil-containing medications as elicited from the history. Despite a normal cough and swallowing reflex in most patients, oil had been aspirated into the lung by a surprisingly large number. It has been demonstrated that mineral oil introduced into the pharynx is capable of entering the bronchial tree without exciting reflex inhibition.[22,23] This has also been shown in animal experiments by demonstrating that liquid petrolatum fails to produce a cough reflex and, therefore, does not stimulate reflex closure of the glottis.[5] In addition, it hinders ciliary activity mechanically by slowing or by stopping the flow of mucus normally promoted by the action of the cilia.[24]

For many years lipoid pneumonia has frequently been an incidental finding at autopsy[14,25] because the clinical signs and symptoms are not characteristic or may be absent and because interpretation of the roentgenograms may be difficult due to the frequently uncharacteristic picture of this condition. In order to facilitate the clinical diagnosis the method of sputum examination previously elaborated by the authors[1] proved helpful in establishing the correct clinical diagnosis in fifty-five of fifty-seven cases. It was confirmed either by aspiration of material from the lung, by roentgenographic studies of the chest or by both methods.

Many of the patients had no signs and symptoms pertaining to pulmonary disease. Others gave a history of intermittent and occasionally productive cough or dyspnea. The latter conditions may in several of the cases be due to associated cardiovascular conditions. It is generally believed that lipoid pneumonia gives no objective clinical signs. However, twenty (35.1 per cent) patients had fine or coarse moist rales primarily in the right lower lobe or over both bases upon auscultation. The majority of the patients revealed no other signs or symptoms of pulmonary disease except lipoid pneumonia.

Our studies suggest that the macrophages frequently disintegrate thus setting free the intracellular lipoid droplets. The liberated lipoid material may be aspirated again from the upper bronchial tree and returned to the alveoli thus producing a vicious cycle by stimulating proliferation of macrophages and eventually causing fibrosis. This may account in part for the chronicity of the process even after oral or nasal intake of lipoid material has long been discontinued. The lack of saponification of mineral oil makes its assimilation and absorption impossible.

It should be stressed that in a considerable number of patients expectoration of lipoid material was sporadic or intermittent. Occasionally, several sputum examinations were required before lipophages were found. Investigation of six patients kept on a fat-free diet for a period of six weeks revealed that the amount of lipoid in daily examination of the sputum varied considerably. In some smears only a small number of lipophages were noted whereas other examinations revealed a considerable amount of intra- and extracellular lipoid material. In two patients the sputum smears were thoroughly searched for five consecutive days before lipoid material was found. Possibly the fibrous connective tissue surrounding the older lesions and the plugging of the alveolar ducts or respiratory bronchioles by inspissated material may prevent continuous discharge of lipoid material which had accumulated in the areas of consolidation.

In fifty-six patients aspiration of material from the lung was done. The procedure has been described previously.[1,26,27] In several cases repeated aspirations had to be performed before evidence of lipoid pneumonia was found. In those patients whose roentgenographic examination showed no pulmonary lesions characteristic of this condition, a point in the ninth intercostal space posteriorly and 3 inches to the right of the spinal column was arbitrarily selected for aspiration. This site was chosen because of the frequency with which in our past experience lesions were found in this location. The only untoward effect encountered in this procedure was an asymptomatic localized pneumothorax in two cases and the aspiration of blood in four patients. In none of these patients did the bleeding cause any major complications except that the sputum remained blood-tinged for three or four days. In one patient in whom suction was not immediately discontinued the procedure was repeated three weeks later and revealed large amounts of lipoid material.

In five patients the previous findings were confirmed at autopsy. In one patient a typical picture of lipoid pneumonia was observed in an area measuring about 2½ by 1½ by 1 cm. located posteriorly at the base of the right lung. This lesion was found only after thorough search and lamellating the lungs. It may well be that a small area of lipoid pneumonia might be overlooked in a case in which this condition is not suspected. So far we have not encountered a case of lipoid pneumonia at autopsy among those patients in whom this condition was excluded during our survey.

It can be concluded that lipoid pneumonia occurs more frequently among the chronically sick patients than is generally believed. The recognition of lipoid pneumonia is particularly important in those patients in whom a diagnosis of bronchogenic carcinoma is entertained since it may subject the patient to needless surgical procedures.[28] There are occasional cases reported[29,30] in which bronchogenic carcinoma was associated with lipoid pneumonia. There has not been a single case of a complicating lung neoplasm in our series although we have followed these patients for many years and a considerable percentage are in the cancer age group. The diagnosis of lipoid pneumonia is also of considerable importance in those conditions which are mistaken for other low grade pulmonary infections or bronchiectasis because the correct identification in these conditions may be helpful as to therapeutic procedures contemplated. Moreover, the spread of the lesion can be prevented by discontinuing further intake of mineral oil or other oil-containing medications when the diagnosis is established at an early stage.

SUMMARY

A survey of 389 chronically ill patients revealed fifty-seven cases (14.6 per cent) of lipoid pneumonia diagnosed by examination of the sputum, aspiration from the lung and roentgenographic studies of the chest. In fifty-five of the patients examined the sputum showed lipophages or abundant amounts of free lipoid material characteristic of lipoid pneumonia. Aspiration from the lung also revealed typical lipoid-containing macrophages. Twenty patients showed characteristic roentgenographic manifestations of lipoid pneumonia. Thirteen revealed retrocardiac changes in lateral, oblique and when indicated, overexposed film studies which were considered to be consistent with oil aspiration pneumonia although the postero-anterior films were negative for such lesions.

A significant number of the patients had a productive cough and positive physical signs most frequently found over the base of the right lower lobe.

Examination of the sputum and, when necessary, of material aspirated from the lung are valuable procedures for making the diagnosis of lipoid pneumonia.

The mechanism of the progressive nature of the disease after discontinuance of the incitant oily factors is suggested as due to reaspiration of disintegrated lipophages.

REFERENCES

1. Losner, S., Volk, B. W., Slade, W. R., Nathanson, L. and Jacobi, M. Diagnosis of lipoid pneumonia by sputum examination. *Am. J. Clin. Path.*, 20: 539–545, 1950.
2. Guiesse-Pellissier, A. Récherches sur l'absorption de l'huile dans le poumon. *Compt. rend. Soc. de biol.*, 83: 809–811, 1920.
3. Corper, H. J. and Freed, H. Intratracheal injection of oil for diagnostic and therapeutic purposes. *J. A. M. A.*, 79: 1739–1742, 1922.
4. Laughlin, G. F. Studies of pneumonia following injections of oil. *Am. J. Path.*, 1: 407–414, 1925.
5. Pinkerton, H. Reaction to oils and fats in the lung. *Arch. Path.*, 5: 380–401, 1928.
6. Rabinovitch, J. and Lederer, M. Lipoid pneumonia. *Arch. Path.*, 19: 160–168, 1934.
7. Graef, I. Pulmonary changes due to aspiration of lipids and mineral oil. *Am. J. Path.*, 11: 862–863, 1935.
8. Ikeda, K. Lipoid pneumonia of adult type (paraffinoma) of the lung: report of five cases. *Arch. Path.*, 23: 470–492, 1937.
9. Pinkerton, H. and Moragues, V. Paraffinoma of the lung with secondary tubercle-like lesions in the liver and spleen. *Arch. Path.*, 29: 691–699, 1940.
10. Sweeney, W. J. Intranasal medication with oils. *Eye, Ear, Nose & Throat Monthly*, 22: 335–338, 1943.
11. Schneider, L. Pulmonary hazard of the investigation of mineral oil in the apparently healthy adult *New England J. Med.*, 240: 284–291, 1949.
12. Even, R. Les pneumopathies huileuses de l'adulte. *Bull. et mém. Soc. Méd. d. Hôp. de Paris*, 70: 78–80, 1947.
13. Facquet, M. J. et Mme. Langeard. Deux cas d'opacités pulmonaires du lobe moyen chez des chanteurs (pneumonie huileuse probable). *Bull. et Mém. Soc. Méd. d. Hôp. de Paris*, 70: 200–204, 1947.
14. Freiman, D. G., Engelberg, H. and Merrit, M Oil aspiration (lipoid) pneumonia in adults. *Arch. Int. Med.*, 66: 33–38, 1940.
15. Sodeman, W. A. and Stuart, H. M. Lipoid pneumonia in adults. *Ann. Int. Med.*, 24: 241–253, 1946.
16. Moel, M. and Taylor, H. K. Oil aspiration pneumonia. *Am. J. Roentgenol.*, 49: 177–184, 1943.
17. Singer, J. J. and Tragerman, L. J. Lipoid pneumonia. *Am. Rev. Tuberc.*, 43: 738–747, 1941.
18. Stokes, A. M. Lipid pneumonia. *Am. Rev. Tuberc.*, 47: 348–350, 1943.
19. Pierson, J. W. Some unusual pneumonias associated with aspiration of fats and oils. *Am. J. Roentgenol.*, 27: 572–578, 1932.
20. Lillie, R. D. Histopathologic Technique. Philadelphia, 1948. The Blakiston Co.
21. Greenwald, H. N., Nathanson, L. and Steiner, M. Chronic pneumonia associated with nutritional disturbances in infants. *Am. J. Roentgenol.*, 35: 454–467, 1936.
22. Quinn, L. H. and Meyer, O. O. Relationship of sinusitis and bronchiectasis. *Arch. Otolaryng.*, 10: 152–165, 1929.
23. Pierie, A. H. In discussion of Pierson, J. W.[19]
24. Proetz, A. W. Effects of certain drugs on living nasal ciliated epithelium. *Am. Otol., Rhin. & Laryng.*, 43: 450–463, 1934.
25. Cannon, P. R. The problem of lipoid pneumonia. *J. A. M. A.*, 115: 2176–2179, 1940.
26. Farber, J. E., Carpenter, R. and Pellicano, V. Lipoid pneumonia: diagnosis by aspiration biopsy. *Am. Rev. Tuberc.*, 45: 453–455, 1942.
27. Nathanson, L., Fraenkel, D. and Jacobi, M. Diagnosis of lipoid pneumonia by aspiration biopsy. *Arch. Int. Med.*, 72: 627–634, 1943.
28. Brown, A. L. and Biskind, G. R. Differential diagnosis between lipoid pneumonia and pulmonary neoplasms. *J. A. M. A.*, 117: 4–6, 1941.
29. Wood, E. H., Jr. Unusual case of carcinoma of both lungs associated with pneumonia. *Radiology*, 40: 193–195, 1943.
30. Sante, L. R. The fate of oil particles in the lung and their possible relationship to the development of bronchogenic carcinoma. *Am. J. Roentgenol.*, 62: 788–797, 1949.

Multiple Myeloma without Demonstrable Bone Lesions*

ROBERT S. WALLERSTEIN, M.D.

Topeka, Kansas

MULTIPLE myeloma is a well defined clinical entity with characteristic findings roentgenologically, in the bone marrow aspirate and on chemical and clinicopathologic examination of the blood and urine which taken together usually suggest the correct diagnosis. Since the first case of "mollities and fragilitas ossium accompanied with urine strongly charged with animal matter" was published by MacIntyre[14] in 1850 and Bence-Jones carried out his now historic investigations of the strange behavior of the "animal matter" in this same patient's urine, numerous other manifestations have been added to the clinical syndrome. At present, in addition to the bone lesions and the Bence-Jones proteinuria originally described a complete clinical picture also includes characteristic roentgen lesions, immature plasma cells of the myeloma cell type in increased numbers and in nests in the smear of the bone marrow obtained by aspiration, anemia, accelerated erythrocyte sedimentation rate, hyperglobulinemia, increased rouleaux formation of the red cells, paramyloid deposits, shift to the left in the peripheral blood count and (rarely) an outpouring of the characteristic cell type into the peripheral blood sufficient to warrant the designation of plasma cell leukemia.

In the period before x-ray, diagnosis rested primarily either on biopsy of palpable tumors, usually of the ribs, or on necropsy with the demonstration of typical plasma cell tumors in either case. In 1905 Wood[26] was able to collect only thirty authenticated cases covering a period of nearly sixty years. With the advent of roentgen examination the number of reported cases multiplied rapidly. In 1928 Geschickter and Copeland[10] reviewed a total of 425 cases including thirteen of their own. This increase in the number of reported cases since the introduction of x-ray diagnosis probably reflected not a proportionate increase in incidence but rather the more frequent employment and increasing accuracy of roentgen methods.[9]

Two types of bone lesions recognizable on x-ray examination were soon delineated. One was the typical multiple discrete lytic lesion without bone production, with a predilection for the cancellous bones of greatest red marrow content (vertebrae, ribs, sternum, clavicle, skull, pelvis and proximal ends of humerus and femur), the so-called "punched-out lesions."[1,2,4,6,7,9,10,12,18,20,21,23] This was the "classic" and better known type of lesion and was correlated with the pathologically evident focal accumulations of myeloma cells in the form of discrete tumor masses. A second type of lesion was likewise described, however, in which the myelomatous process is diffuse throughout the marrow rather than multiple and focal and the corresponding x-ray picture is one of diffuse and generalized decalcification particularly in the vertebral column, with eventual compression and collapse of many of the vertebral bodies and ballooning of the intervertebral discs.[1,4,6,7,10,12,21,23] These cases are often first diagnosed as idiopathic senile osteoporosis. Evidence for myeloma should be sought in all such cases.[1]

The ease and widespread use of roentgen

* From the Second Medical Service of the Mount Sinai Hospital, New York, N. Y.

examination made the x-ray rapidly assume a central position in the establishment of this diagnosis. In 1933 Flax[9] stated that "the value of the roentgen examination in the diagnosis of multiple myeloma is widely acknowledged. . . . Roentgen findings either indicate or confirm the diagnosis. . . history, blood, and urine findings, and the clinical course of the disease, corroborate but scarcely rival the roentgen findings in importance."

Since a marked degree of marrow hyperplasia and bone resorption must be present to be roentgenologically visible, one can assume that there is a stage at the beginning of the disease in which myeloma cells are already present in abundance in the marrow and in which the diagnosis can be made by sternal aspiration but bone resorption is not yet enough advanced to produce demonstrable lesions. That myelomatosis may exist and can be recognized despite completely negative x-ray findings has received but scant attention in the literature.

Passing reference has been made on several occasions, however, and a few cases have been previously described. Thus Moschcowitz[16] stated that "diffuse myelomatosis may occur without positive x-ray evidence as shown by biopsy and especially by sternal puncture." Lichtenstein and Jaffe[13] in a survey of thirty-five cases of which eighteen came to autopsy stated that "sometimes, when myelomatous infiltration of the bone marrow is diffuse, skeletal changes may not be apparent at all roentgenographically in spite of complaints referable to the skeleton." Brailsford's textbook[7] states that "there are cases, with no radiographic evidence of disease, either local or general, to which the diagnosis of myelomatosis is given because sternal puncture of a cachectic patient having Bence-Jones proteose in the urine has yielded material rich in plasma cells." Similar statements but also without offering supporting cases were made by several other authors.[5,11,17] There are in addition several case reports of patients with well established myelomatosis but without x-ray findings although we do not know in most of these how complete the skeletal survey actually was and how many of these patients were subsequently followed up to their termination without development of visible skeletal lesions of either the focal or the diffuse type. Thus Bayrd and Heck[4] in reviewing eighty-three proved cases of multiple myeloma at the Mayo Clinic stated that "In 12% of these cases, no abnormalities of the osseous system whatsoever were demonstrated by roentgenography (all roentgenograms included head, thorax, and spinal column and ⅔ were complete)." Waldenström[23,24] in Sweden described a group of three patients whom he designated as having "incipient myelomatosis or essential hyperglobulinemia with fibrinogenopenia" in all of whom complete skeletal surveys were normal. As pointed out by Ranström[19] these cases in all probability represented patients with multiple myeloma in whom the hyperglobulinemia and the disorders attendant upon it were a dominating part of the clinical picture but who also showed a pathologic plasma cell increase in the sternal marrow (either on aspiration or on subsequent postmortem examination) although the x-ray findings were negative. Ranström[19] stated that "cases with intense hyperglobulinemia without demonstrable chronic infection focus or neoplasm causes the clinician to suspect myelomatosis. If the roentgen examination in such cases yields negative results, it will be the bone marrow puncture that has to decide the issue." Likewise, Tranbøl[22] in Denmark published several cases with no roentgenologically demonstrable bone changes but in which sternal puncture revealed the true nature of the disease, the bone marrow being found diffusely infiltrated with myeloma cells.

In those patients with myeloma who have a sufficient increase in the plasma cells in the circulating blood to warrant the designation of plasma cell leukemia there seems to be a statistically somewhat greater chance that the skeletal system be roentgenologically intact. There are two case reports, one by Bayrd and Hall[3] and one by Meyer et al.,[15]

in which typical marrow and peripheral blood findings were combined with a normal x-ray survey although up to 1946 Moss and Ackerman[17] could collect only thirty-six cases of plasma cell leukemia all told, in many of which no x-ray studies were made. Solitary myeloma which seems to be a related variant of multiple myeloma that usually represents a precursor state before the process becomes disseminated almost always reveals itself as a roentgenologically visible destructive area in some bone. However, there is a single case report of a case[8] in which the tumor manifested itself not as a lytic lesion in bone but, because of its position, by sudden pain in the back and rapid onset of paraplegia. X-ray of the dorsolumbar spine showed arthritic changes with spur formation but "no evidence of bone destruction." Exploration revealed a plasma cell myeloma of T_{11} with intraspinal epidural extension.

From the foregoing sparse references it is apparent that the concept of multiple myeloma without bone lesions, although known and occasionally alluded to, has not gained sufficient currency. The diagnosis may often be overlooked, especially in patients who present themselves with severe bone pain and an obscure anemia, and in whom a negative skeletal survey is taken to be sufficient evidence to dismiss multiple myeloma as the underlying cause. The following three cases, of which two patients were followed up to termination and postmortem examination, are being reported from the series of patients with this diagnosis seen on the wards of the Mount Sinai Hospital within a single year. They are cited as examples of multiple myeloma without bone lesions in order to direct attention to this little known entity and to indicate the importance of sternal marrow aspiration in diagnosis.

CASE REPORTS

CASE 1. This patient, No. 581833, was admitted June 8, 1948, and died August 9, 1948. This was the first Mount Sinai Hospital admission of a fifty-three year old white woman who entered because of pains in the shoulders and legs of one year's duration. The patient was perfectly well until one year before admission when she began to have pains in both shoulders not associated with local swelling or increased heat. The pain was fluctuating in severity and during the periods of acute exacerbation the patient noted limitation of motion of her arms so that she could not raise them over her head. About six months before admission she noted the onset of pain in both knees severe enough to interfere frequently with sleep. The pain spread to involve both legs and because of its severity she became completely bedridden. For three months prior to admission she was confined to bed. She was hospitalized at another New York hospital where numerous skeletal x-rays were taken and sternal marrow aspiration was performed, following which she was transferred to the Mount Sinai Hospital for further study and treatment. She had lost 23 pounds in weight since the onset of her illness.

Physical examination revealed a well developed but apathetic and poorly nourished white female. Her temperature was 99.4°F., pulse 100 and blood pressure 165/85. The skin and mucous membranes were pale and the patient moved in bed with great difficulty. There were no bony lesions over the clavicles or thoracic cage but the ulnar and fibular heads bilaterally were extremely prominent with some periarticular swelling and surrounding soft tissue atrophy. Behind the right knee there was a lemon-sized rubbery mass which seemed to be attached to the underlying bone and a similar smaller mass in the right elbow. The lungs were clear. The heart showed a soft systolic blowing murmur at the apex. The abdomen was normal with no palpable masses or viscera and neurologic examination was negative.

Laboratory examination showed hemoglobin of 9 gm., white blood cell count 11,950 with normal differential, and platelet count of 270,000. The urine showed 3+ albuminuria with sulfosalicylic acid and gave a positive ring test when layered on concentrated HCl. Test for Bence-Jones proteinuria was positive with a precipitate appearing at 48°C. which almost completely dissolved at 85°C. and which reappeared on cooling after filtering at 100°C. to remove precipitated albumin. Stool guaiac was positive 2+. The sedimentation rate was 32 mm./hr. (Westergren). Blood chemical determinations revealed urea nitrogen 40 mg.

per cent, uric acid 7.7, creatinine 4.0, nonprotein nitrogen 53, calcium 13.8, phosphorus 3.4, alkaline phosphatase 11 King-Armstrong units and sugar 100 mg. per cent. Thymol turbidity and cephalin flocculation tests were both negative. Total protein was 5.2 gm. per cent, with 3.1 albumin and 2.1 globulin. Formol-gel test was negative. Phenolsulfonphthalein excretion was 19 per cent in two hours and urine concentration test revealed fixation at 1.010. The blood Wassermann test was negative and the electrocardiogram was normal. X-rays of the skull, dorsolumbar spine and all long bones were reported as follows: "No destruction or sclerotic changes in any of the bones. The spine shows evidence of a hypertrophic spondylitis most marked on the lower dorsal area. The long bones show no abnormality. There are some osteoarthritic changes at several of the joints. The bones of the calvarium are not unusual. The sphenoid ridges and sphenoid fissures appear normal." Biopsy of the tumor mass in the right elbow yielded "fat tissue without significant change." Iliac crest marrow aspiration yielded the characteristic marrow picture of multiple myeloma with many myeloma cells, including many in nests and many binucleate.

On the basis of the clinical picture of anemia with severe bone pain, the marrow finding of numerous myeloma cells, the Bence-Jones proteinuria and the impairment of renal function with moderate retention of nitrogenous products, a diagnosis of multiple myeloma with myeloma kidneys was made. Of interest in this case was the complete absence of any demonstrable x-ray lesions in the bones other than osteoarthritic changes. There were neither the typical punched-out lesions nor the generalized decalcification sometimes seen. The soft tissue tumors in the elbow and behind the knee were not related to bone in any way by x-ray. They were thought to be either myelomatous tumors or amyloid tumors of the type often seen arising from the joint capsule in this disease. However, biopsy revealed only fat tissue.

The patient was started on a course of therapy with stilbamidine, despite which she continued to do poorly. Due to her prolonged bedrest and general debility she developed decubitus ulcers which stubbornly resisted treatment. Numerous blood transfusions were given to combat the anemia and to give the patient general support. She began to show some slight improvement and after six hospital weeks the ulcers were showing signs of healing and it was possible to get her up in a chair. However, in her ninth week there was a sudden dramatic change in her general condition. A purplish mottling with numerous purpuric spots scattered over the entire body, stiffness of the neck and cardiovascular collapse developed. Lumbar puncture revealed fluid under normal pressure but with blood in all tubes. Wassermann, colloidal gold, globulin and culture of spinal fluid were all negative. The possibilities of subarachnoid bleeding or massive adrenal hemorrhage as the cause of the sudden change in the clinical picture were raised. The patient lapsed into coma and died within a few hours. Blood culture taken ante mortem subsequently grew out a diphtheroid in several flasks.

Autopsy findings revealed the following: (1) multiple myeloma, (2) amyloidosis, subendocardial left atrium, myocardium, lung and colon, and amyloid tumor right elbow, and (3) acute bacterial endocarditis (diphtheroid), left auricle with microabscesses of myocardium and kidneys.

Case II. This patient, No. 583285, was admitted July 13, 1948, and died August 5, 1948. This was the first Mount Sinai Hospital admission of a fifty-six year old white woman admitted with chief complaints of abdominal pain, weight loss and burning in her throat. The patient had been well until about eight months prior to admission when following an acute upper respiratory infection with sore throat she noted that her entire mouth began to feel sore and she suffered gradual, complete loss of taste except for sweet foods. All other foods tasted bitter. Her mouth became cracked in the corners and dry with absent saliva so that she had to rinse food down with fluids. Her tongue was sore and a burning sensation was present extending down to the stomach. Dysphagia was severe. During this period dull, constant, epigastric and periumbilical pain developed aggravated by food and relieved by ginger ale. In the four weeks preceding admission she vomited bile-stained fluid every few days and began to notice bright red blood in her stools. Since the onset of the illness eight months before there had been severe anorexia and weight loss of 40 pounds. She had been treated elsewhere with liver, iron, ertron, vitamins and hydrochloric acid, all to no avail. She was thought to have a refractory macrocytic anemia of an ill defined type, with secondary changes of vitamin deficiency.

The patient was found to have a smooth tongue with some hypertrophied papillae and a healing cheilosis. There was mild pallor and some spooning of the fingernails. Her temperature was 99.6°F., pulse 96 and blood pressure 100/60. Her heart and lungs were normal. There was a mild non-significant adenopathy with palpable axillary, submental, posterior cervical and inguinal glands. The abdomen revealed the liver to be four fingers below the costal margin. Pelvic and rectal examinations were negative except for external hemorrhoids.

Laboratory examination showed hemoglobin 10 gm., red blood count 3,350,000, hematocrit 31 per cent, white blood count 9,800 with polymorphonuclears 32 per cent, lymphocytes 54 per cent, abnormal lymphocytes 7 per cent, monocytes 4 per cent, eosinophiles 2 per cent and basophiles 1 per cent. There was slight hypochromia, anisocytosis and poikilocytosis. Platelets were 160,000 and reticulocytes 0.4 per cent; red cell fragility test showed decreased fragility. The urine had a specific gravity of 1.030, albumin 1+ and some white blood cells and red blood cells on microscopic examination. Search for Bence-Jones proteinuria was negative. Sedimentation rate was 4 mm./hr. (Westergren) on one occasion and 26 on another. Stool guaiac was persistently markedly positive. Blood chemical determinations revealed urea nitrogen 13 mg. per cent, uric acid 7.0, creatinine 1.5, non-protein nitrogen 30, sugar 112 and icteric index 2. The thymol turbidity and cephalin flocculation tests were negative. The galactose tolerance test and 3 gm. cinnamic acid test were negative. Alkaline phosphatase was 7 King-Armstrong units, calcium 10.0 mg. per cent and phosphorus 1.6. Total protein was 4.9 gm. per cent, with 2.6 albumin and 2.3 globulin. The formol-gel test, Sia globulin test and cryoglobulin tests were negative. Urine concentrated to 1.022 and phenolsulfonphthalein excretion was 55 per cent in two hours. Electrocardiogram showed evidence of diffuse myocardial damage with QRS of low voltage and prolonged to .12 seconds and T waves of low voltage in all leads. The blood Wassermann test was negative.

On admission the diagnosis was not clear. The patient's symptoms had been mainly burning, dysphagia, cheilosis and weight loss. Moderate anemia was present and some spooning of the nails. It was believed that the patient might have some sort of primary anemia, either pernicious anemia or hypochromic anemia on an iron deficiency basis of the Plummer-Vinson type, but that because of the long and intensive therapy with liver and iron the picture was obscured. Other possibilities which were considered were liver cirrhosis and neoplasm of the gastrointestinal tract with liver metastases. Liver function studies were all negative. There were no collateral signs of cirrhosis or of portal hypertension. Gastric aspiration showed no free acid and blood in all specimens but the gastrointestinal series was normal. Sigmoidoscopy showed a friable mucous membrane with many submucosal and petechial hemorrhages, with some block to the passage of the instrument at 12 cm. This was repeated and the sigmoidoscope passed 21 cm. without block. The friable mucous membrane was again visualized but no neoplasm was found. A barium enema was negative. No evidence for either cirrhosis or neoplasm could be uncovered.

Sternal marrow aspiration was done which revealed numerous typical myeloma cells, many of them in clumps, many binucleate and many in mitosis. On differential count these cells comprised 8 per cent of the nucleated elements. X-rays were then taken of the skull, mandible, chest, thorax, pelvis and long bones which were reported as follows: "Skull: No abnormalities are observed in the bones of the cranial vault. The sella tircica appears normal. Mandible: There are no demonstrable abnormalities in the structure of the bones. The jaw is edentulous. Chest: The ribs and clavicles appear normal. Pelvis: No abnormalities. Long bones: No abnormalities." There were neither punched-out lytic areas nor diffuse decalcification. Despite these negative x-ray findings and the absence of the concomitant abnormalities in protein metabolism often seen in myeloma (hyperglobulinemia and Bence-Jones proteinuria) it was believed that the characteristic bone marrow picture was pathognomonic of this disease entity.

While still being studied and before institution of therapy, the patient suddenly awoke one morning with a complete left hemiplegia, flaccid in type, involving the left arm, leg and left side of face, with some accompanying sensory loss. Lumbar puncture showed clear fluid with normal dynamics. There were no cells. The Nonne reaction, globulin, Wassermann and colloidal gold tests were negative. Protein was 45 mg. per cent. Two days after the onset of the left hemi-

plegia the patient began to complain of dyspnea, tachypnea and precordial pain which were followed with the sudden onset of congestive heart failure with rales at both bases, peripheral edema and a rapidly enlarging liver. Venous pressure was 13 cm. and circulation time 30 seconds. The patient had an abnormal and changing electrocardiogram but nothing characteristic of an acute myocardial infarct. Peripheral edema gradually progressed, more on the paralytic side. Three days after the onset of the congestive failure signs of pneumonia or of pulmonary infarction developed at the left base and two days later back pain developed, radiating down both legs. The patient went rapidly downhill despite supportive therapy and died on the twenty-third hospital day.

Autopsy findings revealed the following: (1) multiple myeloma, (2) amyloidosis of heart, pancreas, gastrointestinal tract, uterus, ovaries and blood vessel walls, (3) mural thrombus right atrium, (4) multiple pulmonary emboli with pulmonary infarctions both lower lobes, bilateral pleural effusions and pulmonary edema, (5) chronic rheumatic heart disease with mitral stenosis and insufficiency and (6) cerebrovascular accident with left hemiplegia.

Case III. This patient, No. 588326, was admitted November 15, 1948. This was the first Mount Sinai Hospital admission of a sixty-eight year old white male who was in good health until one year before admission when he noted the insidious onset of anorexia, weakness and weight loss progressive up to the time of admission. Nine months before admission a dull, persistent pain developed in the lumbosacral region which was treated with physiotherapy as an outpatient in another hospital. The pain gradually subsided completely and did not return. However, his other symptoms continued and six months before admission his family noted increasing pallor. Because of this he entered two other hospitals in both of which work-up did not reveal the cause of the progressive anemia. He was discharged from each without definite diagnosis and was treated with liver, iron and blood transfusions with only temporary improvement. For the two months before admission he also suffered nausea and occasional vomiting along with his progressive weakness, anorexia and pallor. He lost a total of 71 pounds in the last year. However, in the seven months before admission he suffered no pain. He was referred to the Mount Sinai Hospital for further evaluation and treatment. His past history was significant only in that thirty years before admission he had fallen from a scaffolding several stories up and suffered multiple fractures. He was critically ill for several weeks at that time.

Physical examination revealed a chronically ill, pale man with signs of marked weight loss. His temperature was 99.4°F., pulse 60 and blood pressure 130/60. The pharynx was pale. There was no glandular adenopathy. The lungs showed dullness and diminished breath sounds at the left base. The heart revealed a harsh systolic murmur at all valvular areas. The abdomen revealed the liver three fingers below the costal margin and the spleen tip just palpable under the costal margin. Rectal examination was normal. Peripheral pulses were all patent.

Laboratory examination showed hemoglobin 8.7 gm., red blood count 2,860,000, white blood count 6,900 with normal differential, and platelets 210,000. The urine showed a specific gravity of 1.018 and 2+ albumin but was otherwise normal. Search for Bence-Jones proteinuria was repeatedly negative. The Sulkowitch reaction was negative as was the stool guaiac. The sedimentation rate was 145 mm./hr. (Westergren).

Blood chemical determinations revealed urea nitrogen 30 mg. per cent, uric acid 6.2, creatinine 2.5, non-protein nitrogen 43, sugar 76, calcium 13.3, phosphorus 2.2, alkaline phosphatase 23, later 24 King-Armstrong units, acid phosphatase 1 King-Armstrong unit, cholesterol 176 mg. per cent, cephalin flocculation test 4+ and thymol turbidity 3+. Total protein was 6.9 gm. per cent, the albumin being 2.2 and the globulin elevated to 4.7. The formol-gel test was positive in six hours. Cryoglobulin was negative. The urine concentrated to 1.018 on only one occasion and the phenolsulfonphthalein excretion was only 25 per cent in two hours. The blood Wassermann test was negative and an electrocardiogram normal with sinus bradycardia and left axis deviation.

Sternal marrow aspiration showed numerous characteristic myeloma cells, many in nests. On differential count they comprised 11 per cent of the nucleated elements. X-ray survey of the skeleton including chest, long bones, spine and pelvis was reported as follows: "There are no stigmata of multiple myeloma in any of the bones examined. There is a lesion of the right fifth rib anteriorly which is expressed as an area of bone dissolution with fairly sharp margins about which there is a soft tissue mass. This

finding is quite compatible with the single type of myeloma. There are marked hypertrophic changes in the dorsolumbar spine with no significant vertebral collapse. There is no bone demineralization. Old fractures of the lower left ribs, left inferior glenoid lip, and upper left fibula show complete bone union."

In view of the characteristic sternal marrow aspirate, hyperglobulinemia, positive formol-gel test, very high sedimentation rate, anemia and moderate degree of renal impairment, a diagnosis of multiple myeloma with myelomatous kidney was made. It was not definitely known whether the single x-ray lesion seen on the right fifth rib represented a myelomatous lesion or an amyloid tumor as is seen not uncommonly in patients with multiple myeloma. Its subpleural position precluded easy biopsy. In any case there were no focal lytic areas nor any evidence of diffuse decalcification. The patient was started on therapy with stilbamidine and supportive blood transfusions. In view of the general poor prognosis the patient's relatives refused to allow completion of the therapy and signed him out of the hospital.

COMMENTS

These three patients, all with bone marrow aspirates characteristic of multiple myeloma, presented a variety of clinical pictures and of diagnostic problems. In each, however, complete x-ray study of the skeleton revealed no clue to the correct diagnosis. The first patient came in with the characteristic but non-specific triad of (1) severe and incapacitating bone pain, (2) progressive anemia and (3) weight loss. These findings together with the presence of definite Bence-Jones proteinuria and impaired renal function suggested the proper diagnosis even before the substantiating marrow aspiration was performed. Of interest was the absence of any demonstrable bony lesions, either focal or diffuse, although the patient had very severe and unrelenting bone pain and in other respects had a well established and advanced myeloma which carried her to her death within two months. One other point of real interest in this case was the nature of the two tumor masses, in the right elbow and behind the right knee. Negative x-ray findings excluded myelomatous tumors arising from within the bone. Biopsy was unsatisfactory but postmortem examination revealed them to be amyloid tumors such as occasionally arise from the joint capsules in patients with multiple myeloma. In addition the patient also had amyloid in her colon, lung and heart.

The second patient represented a much more difficult diagnostic problem. In that patient the bone marrow aspiration represented the first and during life the only indication of multiple myeloma. The patient did not suffer pain either before admission or at any time in the hospital. Her chief complaints on admission were (1) progressive anemia, (2) weakness and weight loss and (3) dysphagia and cheilosis. These findings together with the spoon nails found on physical examination had originally suggested the diagnosis of a primary, hypochromic, iron deficiency anemia of the Plummer-Vinson type. Multiple previous therapies obscured the value of the various hematologic indices at the time of Mount Sinai admission. Evidence for pernicious anemia, liver cirrhosis with avitaminoses and metastatic malignancy was looked for and not found. Sternal marrow aspiration done in order to elucidate the underlying nature of the anemia revealed the true state of affairs. The marrow was characteristic of multiple myeloma, yet the patient had no bone pain whatsoever and thorough skeletal x-ray study was completely negative. The patient suffered in rapid succession left hemiplegia and partial hemisensory, congestive heart failure, pulmonary infarctions and evidence of deep vein thrombosis in the legs. At autopsy in addition to myeloma diffuse amyloidosis of the heart was found, extensive enough to account for the clinical picture of severe progressive cardiac failure. This association of primary amyloid or paramyloid with multiple myeloma as shown in both of these autopsied cases has been long noted in the literature[12,13] and the heart has been one of the favorite localizations of this process. Lichtenstein and Jaffe[13] state that "so often is multiple myeloma the

basis for so-called atypical or idiopathic amyloidosis that the possibility of myeloma should be investigated in every case even though the bones present no apparent evidence of tumor either roentgenographically or on gross inspection at autopsy." The second case reported fits well into this category.

The third patient presented a still different group of clinical signs. Although he had had some lumbosacral back pain about a year before admission, this had disappeared shortly thereafter; and at the time of admission his complaints were (1) anemia and weakness and (2) weight loss of 71 pounds in one year but no pain. In this patient more of the abnormalities of protein metabolism popularly associated with this disease were present and, therefore, again the diagnosis could be suggested prior to marrow aspiration. The anemia was profound (hemoglobin 8.7 gm.) and the sedimentation rate was extremely rapid (145 mm./hr.). The total protein was normal (6.9 cm. per cent) but marked hyperglobulinemia (4.7 gm. per cent was present. The formol-gel test was positive. There was moderate renal insufficiency but there was no Bence-Jones proteinuria. There was no bone pain and the alkaline phosphatase was elevated to 23 and 24 King-Armstrong units on two determinations which also is most unusual for a patient with multiple myeloma. In over twenty patients with this diagnosis on the wards of the Mount Sinai Hospital this past year no other had an elevated alkaline phosphatase. Here, too, accurate diagnosis depended on the marrow aspiration which again in this case presented the characteristic picture. Complete x-ray studies were fruitless with the single exception of a lesion visualized on the right fifth rib anteriorly. This might be a solitary myeloma (a focal collection of the same cells scattered so diffusely through the marrow). Its position precluded easy biopsy.

SUMMARY

Three patients are presented with a great variety of complaints and collateral signs, in all of whom a definite diagnosis of multiple myeloma was made on the basis of characteristic findings by bone marrow aspiration. All had negative skeletal x-ray surveys showing neither the classic focal, punched-out, lytic lesions nor the diffuse decalcification sometimes seen.

In two of these patients autopsy subsequently confirmed the diagnosis of multiple myeloma and revealed associated amyloid deposits particularly in the heart.

Wider use of bone marrow aspiration as a diagnostic tool in patients with obscure anemia, pain, weight loss, etc., would probably result in more cases of multiple myeloma being recognized.

REFERENCES

1. Aegerter, Ernest and Robbins, Robert. The changing concept of myeloma of bone. *Am. J. M. Sc.*, 213: 282–289, 1947.
2. Atkinson, F. R. B. Multiple myelomata. *M. Press*, 195: 312–317, 327–333, 1937.
3. Bayrd, Edwin D. and Hall, Byron E. Unusual remission after radiophosphorus therapy in a case of "acute plasma cell leukemia." *Blood*, 3: 1019–1024, 1948.
4. Bayrd, Edwin D. and Heck, Frank J. Multiple myeloma. A review of eighty-three proved cases. *J. A. M. A.*, 133: 147–157, 1947.
5. Bichel, Jorgen and Kirketerp, Poul. Notes on myeloma. *Acta radiol.*, 19: 487–503, 1938.
6. Blaine, E. S. Myelomatosis with special reference to the roentgenological features. *Radiol. Rev.*, 4: 6–9, 1927.
7. Brailsford, James F. The Radiology of Bones and Joints, pp. 704–706, 4th ed. 1948. Baltimore, 1948. Williams & Wilkins.
8. Cabot Case No. 26072. *New England J. Med.*, 222: 274–276, 1940.
9. Flax, Nathan. Multiple myeloma. An evaluation of its roentgen signs. *Am. J. Roentgenol.*, 29: 479–486, 1933.
10. Geschickter, Charles F. and Copeland, Murray M. Multiple myeloma. *Arch. Surg.*, 16: 807–863, 1928.
11. Ghormley, Ralph K. and Pollack, George A. Multiple myeloma. *Surg., Gynec., & Obst.*, 69: 648–655, 1939.
12. Kolff, W. J. and Dhont, J. Plasmacytoma (multiple myelomas, Kahler's disease) and its attendant disturbances in the protein metabolism. *Am. J. M. Sc.*, 215: 405–410, 1948.
13. Lichtenstein, Louis and Jaffe, Henry L. Multiple myeloma. A survey based on thirty-five cases eighteen of which came to autopsy. *Arch. Path.*, 44: 207–246, 1947.
14. MacIntyre, William. Case of mollities and fragilitas ossium accompanied with urine strongly charged with animal matter. *Med.-Chir. Tr.*, 33: 211–232, 1850.

15. Meyer, Leo M., Halpern, Jacob and Ogden, Faith N. Acute plasma cell leukemia. *Ann. Int. Med.*, 22: 585–598, 1945.
16. Moschcowitz, Eli. Essays on the Biology of Disease. Chapt. 16, Myeloma. *J. Mt. Sinai Hosp.*, 13: 205–211, 1946.
17. Moss, William T. and Ackerman, Lauren V. Plasma cell leukemia. *Blood*, 1: 396–406, 1946.
18. Pillmore, George Utley. Clinical Radiology. A Correlation of Clinical and Roentgenological Findings., vol. II, p. 614. Philadelphia, 1947. F. A. Davis Co.
19. Ranström, S. On the terms "essential hyperglobulinemia" and "premyeloma." *Acta med. Scandinav.*, 124: 134–147, 1946.
20. Shanks, S. Cochrane, Kerley, Peter and Twining, E. W. A Text-book of X-ray Diagnosis. By British Authors, Vol. III, pp. 630–632. London, 1939. H. K. Lewis & Co., Ltd.
21. Snapper, I. Medical Clinics on Bone Diseases: A Text and Atlas. New York, 1943. Interscience Publishers, Inc.
22. Tranbøl, Kristian. Diagnosen af Myelomatose. *Ugesk. f. læger*, 32: 847–851, 1937. Quoted by Bichel and Kirketerp.
23. Waldenström, Jan. Die Frühdiagnose der Myelomatose. *Acta chir. Scandinav.*, 87: 365–379, 1942.
24. Waldenström, Jan. Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia—a new syndrome. *Acta med. Scandinav.*, 117: 216–247, 1944.
25. Waldenström, Jan. Some remarks on the previous paper by S. Ranström. *Acta med. Scandinav.*, 124: 148–159, 1946.
26. Wood, Francis Carter. Chemical and Microscopical Diagnosis, pp. 509–510. New York and London 1905. D. Appleton & Co.

Review

Chronic Cyanosis*

ARTHUR SELZER, M.D.
San Francisco, California

LUNDSGAARD and Van Slyke's monograph on cyanosis[1] (1923) summarized modern knowledge of the subject and for almost a quarter of a century remained unchallenged as the authoritative source of information. Within the past few years, however, interest in cyanosis has been revived and greatly intensified. Newer developments responsible for this include the spectacular reduction in the degree of cyanosis in certain congenital malformations of the heart effected by a surgical operation connecting a large systemic artery with a branch of the pulmonary artery.[2] Taussig and Blalock,[3] the originators of this operation, suggested that the schema of Lundsgaard and Van Slyke be widened to include an additional factor in the production of cyanosis, namely, "inadequate circulation to the lungs." Furthermore, the introduction of venous catheterization of the heart provided a new method for the study of the circulation which opened entirely new fields: thus cardiac output was measured by the direct use of the Fick principle; the presence of intracardiac shunts was confirmed directly and their volume estimated; and the concept of pulmonary hypertension found direct confirmation by pulmonary pressure measurements. These are but a few of the recent developments bearing on the subject of cyanosis. In addition, arterial anoxemia was extensively studied during the war years and new tools for its investigation were introduced.

Cyanosis is a sign of great clinical import. Since it always indicates an abnormal quantity of non-oxygen-bearing hemoglobin in the peripheral capillaries, it may have far reaching implications for the physiology of the organism. In the light of recent observations and suggested revisions in the classic concept of its mechanism a review of the status of present knowledge appears desirable. It is the purpose of this communication to examine available evidence bearing on the production of cyanosis and to attempt to bring into harmony the anatomic and physiologic data derived from the most completely studied cases reported in the literature. In order to accomplish this purpose it was necessary to confine the analysis principally to cases of chronically persistent cyanosis in which the information derived from both clinical and pathologic studies could be correlated. Acute, transient and localized forms of cyanosis, as well as those due to methemoglobinemia and sulphemoglobinemia, have therefore not been included in the discussion.

CLASSIC CONCEPT OF THE MECHANISM OF CYANOSIS

Cyanosis is the bluish color of the skin, mucosae and other tissues caused by the presence of an increased quantity of reduced hemoglobin in the capillaries. Lundsgaard[4,5] showed that cyanosis is dependent on the absolute concentration of reduced hemoglobin rather than on the ratio of reduced to oxygenated hemoglobin. In normal individuals under basal conditions there are about 15 gm. of hemoglobin in 100 cc. of blood. Since each cc. of oxygen combines with 0.75 gm. of hemoglobin, the average oxygen capacity of human blood is 20 volumes per cent. In arterial blood 19 of

* From the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

these 20 volumes are combined with oxygen, hence its saturation is 95 per cent. In the mixed venous blood 14 volumes per cent are oxygenated (70 per cent saturation). Since cyanosis is not related to the quantity of oxygenated hemoglobin but to the reduced fraction, it is convenient to speak in terms of "oxygen unsaturation," which is equivalent to the content of reduced hemoglobin in the blood. Thus normal oxygen unsaturation in the arterial blood (A) is 1 volume per cent, that of the venous blood (V) is 6 volumes per cent. Lundsgaard contended that the oxygen unsaturation of the capillaries of the skin is the mean of the arterial and venous values, hence it would be in health $\frac{A+V}{2}$, or 3.5 volumes per cent. If the level of capillary unsaturation increases to about 6 or 7 volumes per cent, cyanosis generally becomes apparent. This threshold is independent of the content of oxyhemoglobin.

According to Lundsgaard and Van Slyke four factors may be operating in the production of cyanosis. These are: factor T, the total content of hemoglobin: factor D, the amount of hemoglobin deoxygenated in the passage of blood from arteries to veins: factor l, the fraction of total hemoglobin passing in reduced form through aerated portions of the lungs: and factor α, the fraction of the total hemoglobin shunted through unaerated channels from the right heart to the peripheral arteries.

Each of these four factors if abnormally high may produce cyanosis. Usually they appear in combination. In addition to these principal factors, there are "modifying factors" which cannot *per se* cause cyanosis but influence to an important extent its presence and severity, making it more easy or more difficult to detect in various individuals or in different parts of the body. These include the number and size of capillaries, the thickness of the epidermis, skin pigmentation and the gradient of desaturation of oxygen in the capillary blood, which can make the hemoglobin in the visible capillaries more or less unsaturated than the mean value derived from the equation.

In physiologic terms, abnormally high factors l and α lead to arterial anoxemia ("anoxic anoxemia") affecting primarily the unsaturation of A in the equation, with the V increased in proportion if oxygen utilization is the same as normal. Factor D increases the arteriovenous oxygen difference ("stagnant anoxemia") in the capillaries, thus in pure form A is normal and V is high. Factor T is seldom operative alone: in polycythemia vera the ratio of oxyhemoglobin to reduced hemoglobin may be normal so that no physiologic disturbance takes place, but the absolute values of A and V may be increased to a point where cyanosis becomes visible. Arterial anoxemia due to factors l or α usually increases secondarily the T and D which are part of adaptive changes, yet at the same time they contribute to the development of cyanosis. The clinical manifestations of these secondary changes, polycythemia and clubbing of digits are important signs providing objective evidence of chronic anoxemia. (Fig. 1-II, III and IV.)

CYANOSIS AS A CLINICAL SIGN

Cyanosis is a clinical sign the recognition of which depends on the visual impression of the observer, and which cannot be presented in any objective or quantitative way. As with most other such signs its recognition is subject to very considerable variation and inaccuracy. The unreliability of the recognition of cyanosis has been recently emphasized by Comroe and Botelho[6] who found a wide range of disagreement among clinicians as to the presence and degree of cyanosis. Such variations among observers are not limited to cyanosis but have been demonstrated in the interpretation of findings of many other diagnostic methods.[7] Cyanosis, however, has an especially wide border zone between normal and abnormal. This is due to a number of factors: (1) the intrinsic modifying factors of Lundsgaard; the recognition of cyanosis depends on the

estimation of the color of blood in the capillaries: the number of these capillaries per square millimeter, and the physical properties of all the media between the observer's eye and the blood profoundly affect the visual impression. (2) Extrinsic factors such as the type of lighting and the background against which the patient is inspected; (3) The fact that cyanosis under certain circumstances is a physiologic phenomenon: persistent cyanosis of extremities, acrocyanosis, may be constitutional with certain individuals and families; cold weather brings about cyanotic appearance of the skin in many healthy individuals; finally, in children cyanosis of considerable extent may be normally visible during crying.

For these reasons only fully developed, severe cyanosis can be considered reliable when reported. Milder degrees of cyanosis may be inaccurately reported, their presence and degree being subject to considerable variations in interpretation. Such cases can be accepted, however, as cyanotic if secondary changes, polycythemia and clubbing are found.

A more accurate estimate of the degree of cyanosis may be made due to the fact that the clinically significant forms of cyanosis are caused by anoxemia (factors l and α). Thus, determination of the arterial oxygen saturation provides an objective guide. It should be emphasized, however, that cyanosis and anoxemia are not synonymous, and the relationship between them is only approximate. The threshold of cyanosis, i.e., the point at which most observers would agree that an individual is cyanotic, may occur in some cases at an 80 per cent level of arterial oxygen saturation, in others at 60 per cent. This is due to the secondary and modifying factors already discussed. The fact that with the same degree of anoxemia one individual may be severely cyanotic and another not at all emphasizes the point that blood saturation determina-

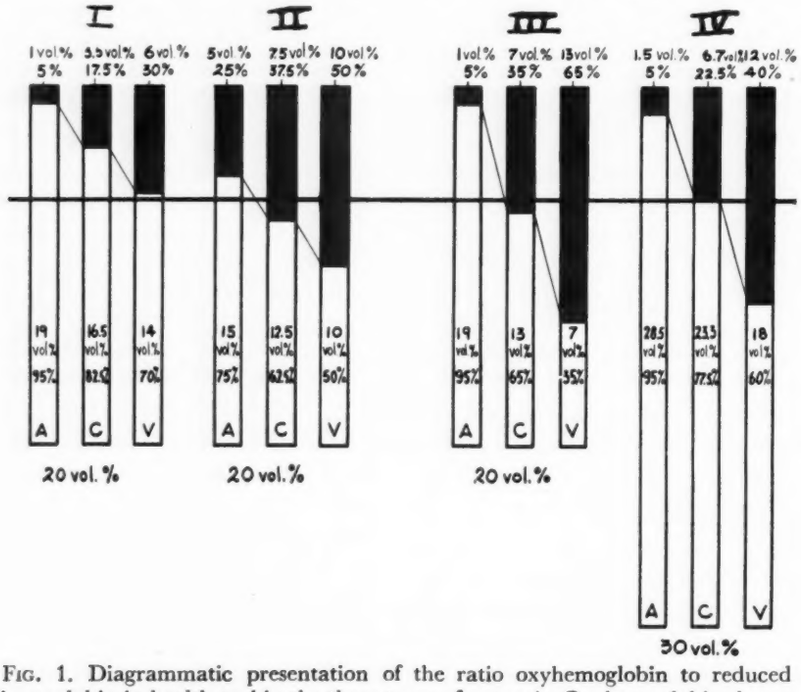


FIG. 1. Diagrammatic presentation of the ratio oxyhemoglobin to reduced hemoglobin in health and in the three types of cyanosis. Oxyhemoglobin shown white; reduced hemoglobin black. I, normal; II, anoxemic cyanosis; III, stagnant cyanosis; IV, polycythemic cyanosis. Column A, arterial blood; C, capillary blood; V, venous blood. Both contents and percentage of saturation (or unsaturation) of hemoglobin and reduced hemoglobin are indicated. The horizontal black line represents the average threshold of visible cyanosis (according to Lundsgaard and Van Slyke).

tions and oxymetric studies do not actually express the degree of cyanosis. Actually, anoxemia is considerably more important than cyanosis. It would be preferable, for instance, to classify congenital heart disease into forms with and without anoxemia rather than into cyanotic and non-cyanotic groups.

CLASSIFICATION OF CYANOSIS

Lundsgaard and Van Slyke[1] emphasized the complex nature of the pathogenesis of cyanosis, pointing out the interrelationship of various factors. It is, however, important to appreciate the fact that cyanosis is almost always due to a single disturbance of physiologic function, while other factors appear secondarily. It will be shown in the subsequent discussion that a partial or total correction of this primary or initiating disturbance leads to prompt disappearance of the secondary factors. It is, therefore, of the utmost practical importance to know the initiating factor in the production of cyanosis. Clinicians have long learned to distinguish "central" cyanosis from the "peripheral" type, and Sir Thomas Lewis[8] suggested a simple bedside way of distinguishing the two types: acceleration of peripheral flow by application of heat or by massaging a cyanotic part of the body abolishes peripheral cyanosis, but central cyanosis persists.

It seems desirable, however, to go further in a search of the primary disturbance leading to cyanosis. In an attempt to separate clinical types of cyanosis according to the primary physiologic disturbance, the following classification of cyanosis is proposed.

Type I. Anoxemic cyanosis due to veno-arterial shunts. Criteria: lowered oxygen saturation of arterial blood; normal oxygen saturation of blood returning from the lungs.

Type II. Anoxemic cyanosis due to pulmonary factors. Criteria: lowered arterial oxygen saturation; lowered oxygen saturation of the blood returning from the lungs: (1) anoxemia due to lowered barometric pressure; (2) anoxemia due to ventilatory insufficiency of the lungs;[9] (3) anoxemia due to alveolorespiratory insufficiency;[9] (4) anoxemia due to perfusion of unaerated sections of the lungs; (5) anoxemia due to intrapulmonary blood shunts (pulmonary arteriovenous fistula).

Type III. Stagnant (peripheral) cyanosis. Criteria: normal arterial oxygen saturation; increased arteriovenous oxygen difference.

Type IV. Polycythemic cyanosis. Criteria: normal values of arterial and venous oxygen saturation expressed in percentage; high absolute amount of reduced hemoglobin enough to cause visible cyanosis.

I. CYANOSIS DUE TO VENO-ARTERIAL SHUNTS

This type is associated with congenital malformations in which there is an abnormal communication between the two sides of the heart or the great vessels. This is the most important group of conditions associated with chronic cyanosis, as in it cyanosis reaches the highest intensity and may persist for the longest periods. The cause of cyanosis in congenital malformations of the cardiovascular system has been considered by Lundsgaard and Van Slyke[1] and by Maude Abbott[10] as being due to veno-arterial blood shunts. The important problem is to decide whether recent developments compel us to revise this classical view and whether important exceptions to it have actually been proven.

In examining critically the suggested revisions it is necessary to try to correlate the presence of cyanosis with the anatomically evident factors offering adequate explanation for it in the light of recent studies of the dynamics of the circulation.

A. ANATOMIC BASIS FOR CYANOSIS

A brief presentation of the path of the circulation as it can be reconstructed at the autopsy table in the better known congenital syndromes is offered.

Malformations Associated with Severe Cyanosis

The group of transpositions of the great arterial trunks: Here the aorta originates mostly or entirely from the right ventricle, the pulmonary artery arises from the left ventricle or from

the right ventricle, or from both. The aorta then carries unoxygenated blood, and in complete transposition the pulmonary artery returns oxygenated blood to the lungs. Obviously, survival is possible only if oxygenated blood can find its way into the arterial system. This may take place through the following connections between the two systems: defects in the ventricular or atrial septa, a widely patent foramen ovale, a patent ductus arteriosus. Cyanosis in the transpositions is often extreme; in general, the wider the connections between the two systems the less intense is cyanosis and the better chance there is for survival beyond infancy. In cases in which the ductus carries a large volume of oxygenated blood into the thoracic aorta the intensity of cyanosis is much greater in the upper part of the body than in the lower.[11]

Tricuspid atresia in which there is a non-functioning rudimentary right ventricle: In this malformation all the venous blood returning to the right auricle is shunted through the foramen ovale to the left heart. Associated with this malformation may be pulmonary atresia or transposition of the arterial trunks. In general, there is a mixture of arterial and venous blood in the left heart and this mixture then flows directly to the aorta, or in some instances through the ventricular septal defect into a transposed aorta. This mixed blood also returns to the lungs through a pulmonary artery or a ductus or the bronchial arteries.

Pulmonary atresia in which there is a ventricular septal defect with an over-riding aorta, or a patent foramen ovale, or both: All the venous blood has to enter the left heart and mix with oxygenated blood, or enters the aorta directly. The aorta collects all the blood from both ventricles and carries part of it to the peripheral vessels, part back to the lungs through a ductus and bronchial arteries.

Aortic atresia: This is a rare defect in which all the oxygenated blood is shunted to the right heart through a ventricular or auricular septal defect where it mixes with the venous blood. This mixture enters the pulmonary artery and hence a part of it enters the ductus arteriosus and through it the aorta. In some cases there is also mitral atresia.

These four types of malformation represent the most serious deviations from the normal course of the circulation of the blood which are consistent with life. The basis for extreme cyanosis is apparent, for venous blood is not merely shunted to the arterial side of the heart but *all* of the venous blood has to enter some segment of the heart from which the peripheral blood eventually has its source.

Malformations Usually Accompanied by Moderate Cyanosis

Trilocular heart: A complete or almost complete absence of one of the cardiac septa (in rare instances both—bilocular heart) may be associated with otherwise normal arterial and venous ostia, or combined with stenosis of one of them, or with transposition of the trunks. In cases of trilocular heart there is a single chamber in which venous and oxygenated blood may mix. The degree of such mixing varies; in some cases cyanosis was reported as minimal[12] it being presumed that streamlining of the blood caused most of the venous blood to reach the pulmonary artery, and oxygenated blood the aorta. Complicating malformations may aggravate cyanosis.

Common arterial trunk: The aorta and the pulmonary artery are fused into a single vessel which originates from both ventricles, overriding a septal defect. This vessel gives up the pulmonary arteries and then pursues the usual course of the aorta. Free mixing of oxygenated and venous blood takes place in the common vessel and explains cyanosis.

Pulmonary stenosis: This is the commonest and most important malformation, often permitting survival to adult age. It was in connection with pulmonary stenosis that the concept of "decreased circulation to the lungs" was advanced and the Blalock-Taussig operation devised. The pathogenesis of cyanosis associated with pulmonary stenosis was investigated by Selzer and Carnes[13] who attempted to correlate cyanosis with anatomic findings.

There are three forms of malformation in which pulmonary stenosis plays a dominating role: (1) Tetralogy of Fallot, the commonest form, is a combination of pulmonary stenosis with a ventricular septal defect and an overriding aorta. The presence of pulmonary stenosis causes the venous blood to enter the over-riding aorta and/or the left ventricle through the septal defect. Thus the anatomic basis for a veno-arterial shunt is obvious. (2) Pulmonary stenosis with patent foramen ovale,[14] in which the ventricular septum is closed, has been shown to be accompanied by severe cyanosis. The

foramen ovale is believed to provide a pathway for the veno-arterial shunt. Dependence of cyanosis on the size of the foramen and the degree of pulmonary stenosis was demonstrated, thus providing an anatomic basis for a veno-arterial shunt.[13] (3) Pulmonary stenosis with closed septa was thought in the past to be a mildly cyanotic form of congenital heart disease with cyanosis caused by peripheral stasis.[10] However, a critical review of all available autopsied cases of this lesion showed that evidence of the existence of cyanosis is not convincing and that in the overwhelming majority of cases of severe pulmonary stenosis with closed septa cyanosis was absent.[13] It was concluded that this condition is not accompanied by cyanosis in uncomplicated cases.

Tricuspid stenosis: This condition is cyanotic only if a patent foramen ovale permits a veno-arterial blood shunt. The course of the circulation is similar to pulmonary stenosis with patent foramen ovale.

In this group of malformations cyanosis is generally milder than in the first group and the prognosis is somewhat better. The anatomic basis of cyanosis is apparent, for in the first two conditions opportunity is provided for the free mixing of venous and oxygenated blood, while in the last two lesions obstruction in the right side of the heart leads to a true veno-arterial blood shunt.

Malformations in Which the Anatomic Basis for Cyanosis Is Less Obvious

The Eisenmenger complex: This syndrome consists of a high ventricular septal defect with the aorta over-riding the defect and coming into contact with the cavities of both ventricles. Cyanosis often appears later in life than in the tetralogy of Fallot, nevertheless it is almost invariably present and may be moderately severe. The difficulty in accounting for the presence of cyanosis on the basis of veno-arterial blood shunt is due to the fact that clinical and pathologic evidence points to a large volume of the pulmonary circulation, such as is usually seen when large quantities of blood enter the right heart from the left side. This appears inconsistent with the postulated presence of a large volume of venous blood in the arterial system, and some observers[3,15] have suggested incomplete pulmonary oxygenation rather than shunt to be the primary factor in the production of anoxemia and cyanosis. It is believed, however,[16] that such a new factor need not be introduced, and that the aorta may receive blood from both ventricles and thus contain enough venous blood to cause cyanosis even though the preponderant flow of blood in the ventricular septal defect is from left to right.

Ventricular septal defect: In isolated ventricular septal defects higher pressure in the left ventricle forces oxygenated blood into the right ventricle so that cyanosis is absent as a rule. There are, however, rare instances in which cyanosis has been reported. A critical review of this subject[17] revealed that these cyanotic cases may well have been cases of the Eisenmenger complex, which is identical with large ventricular septal defects save for the dextroposed aorta. It was pointed out that mild dextroposition of the aorta may be difficult to determine and that a gradual transition exists between cases of isolated ventricular septal defects and the Eisenmenger syndrome. In borderline cases pathologists may disagree as to the precise classification in these two categories.

Atrial septal defect: This syndrome is non-cyanotic as a rule although quantitative studies of arterial oxygen saturation frequently reveal mild arterial anoxemia. This is thought to be due to free mixing of venous and arterial blood in the defect, which leads to anoxemia even though there is a large left-to-right shunt through the defect.[18] Occasionally persistent cyanosis is present, which is explained in the same manner.

Common atrioventricular canal: This is a combination of atrial and ventricular septal defect with the tricuspid and mitral leaflets fused into a common valve. Cyanosis is usually absent, and if present can be explained by mixing of venous and oxygenated blood as in the preceding defect.

Patent ductus arteriosus: The very rare occurrence of cyanosis in this common syndrome is thought to be due to a complicating factor elevating the pressure in the pulmonary artery to a point where there is reversal of the direction of flow in the duct.[19] This may be associated with coarctation of the aorta in which case cyanosis may be limited to the lower part of the body.[20]

In this group cyanosis is milder than in the two preceding categories, or appears only occasionally. The anatomic basis of cyanosis is less obvious but the morphologic

appearance of the defect is such that a veno-arterial shunt is probable, or at least possible.

B. PHYSIOLOGIC BASIS FOR CYANOSIS

It has been shown that on morphologic grounds one is fully justified in classifying cyanosis associated with congenital heart disease as "central cyanosis due to shunt." Not only is there a communication present through which venous blood can enter the systemic arterial circulation, but circumstances can usually be found which make it more likely that more blood flows through such connections from right to left than from left to right. Furthermore a broad but definite relationship can be found between the structural defect and the intensity and frequency of cyanosis: thus the most severe cyanosis is present in cases in which *all* the venous blood has to pass through a segment of the heart from which the aorta originates; less severe cyanosis is found in cases in which *some* of the venous blood is mixed with oxygenated blood before the latter reaches the aorta; finally, inconstant cyanosis occurs in lesions in which evidence favors a left-to-right shunt which could be reversed under special circumstances.

More direct confirmation of intracardiac shunts has become available with the use of newer methods for the study of the cardiovascular system. Left-to-right shunt can be demonstrated by venous catheterization of the heart since highly oxygenated blood is found in the right heart. Right-to-left shunt can be shown by the use of contrast angiocardiography since opacified blood can be shown to enter the aorta from the right ventricle, bypassing the pulmonary circulation. Furthermore, high pressures which were postulated on the right side of the heart in the presence of veno-arterial shunts can now be directly demonstrated by catheterization.

It is thus seen that not only morphologic evidence but also physiologic confirmation of the concept of venous-arterial shunt is available. Two questions remain for consideration in connection with the pathogenesis of cyanosis caused by congenital malformations of the heart: (1) Is there any evidence that central factors other than shunt play a part in the production of cyanosis? (2) What is the rationale for the suggested revision of the Lundsgaard and Van Slyke schema?

The answer to the first question can be simply presented by stating that any factor other than venous arterial shunt has to lead to unsaturation of pulmonary venous blood. Evidence that in congenital heart disease pulmonary oxygenation is incomplete has never been presented. On the contrary, there is excellent evidence that blood returning from the lungs is completely oxygenated. Handelsman et al.[21] reported that in sixteen cases of congenital heart disease (details not available) pulmonary venous blood was completely oxygenated. Dexter et al.[22] drew samples of "pulmonary capillary blood" which was thought to approximate in oxygen content the pulmonary venous blood. In his samples taken from cases of the tetralogy of Fallot oxygen saturation was normal. Bing et al.[23] accepted complete pulmonary oxygenation as an established fact and assumed an arbitrary value of 95 per cent for pulmonary venous blood in their formulas. While full pulmonary oxygenation is generally accepted in the tetralogy of Fallot, other malformations were thought to be associated with incomplete pulmonary oxygenation, namely, the Eisenmenger complex and atrial septal defect. The reason for this assumption was the frequent demonstration of pulmonary vascular disease associated with these syndromes. Yet critical review of the evidence[16,18] shows that it is more reasonable to consider veno-arterial shunt as the cause of cyanosis in these cases also and pulmonary factors need not be present. Furthermore, in atrial septal defects direct proof of complete pulmonary oxygenation is available.[18]

It has been repeatedly argued that the response of a cyanotic patient to breathing of 100 per cent oxygen could help determine the mechanism of cyanosis. It was thought that oxygen breathing could abolish anox-

emia and cyanosis if these were due to incomplete pulmonary oxygenation but should not affect anoxemia if it were due to shunt.[3,15] On this basis a pulmonary factor was thought to be present in the tetralogy of Fallot, and the importance of the shunt was denied in the Eisenmenger complex. However, recent oxymeter studies have invalidated this reasoning. It has been shown that oxygen saturation of the arterial blood rises even in normal individuals[24] and that arterial anoxemia is lessened by oxygen breathing regardless of its cause.[25–27]

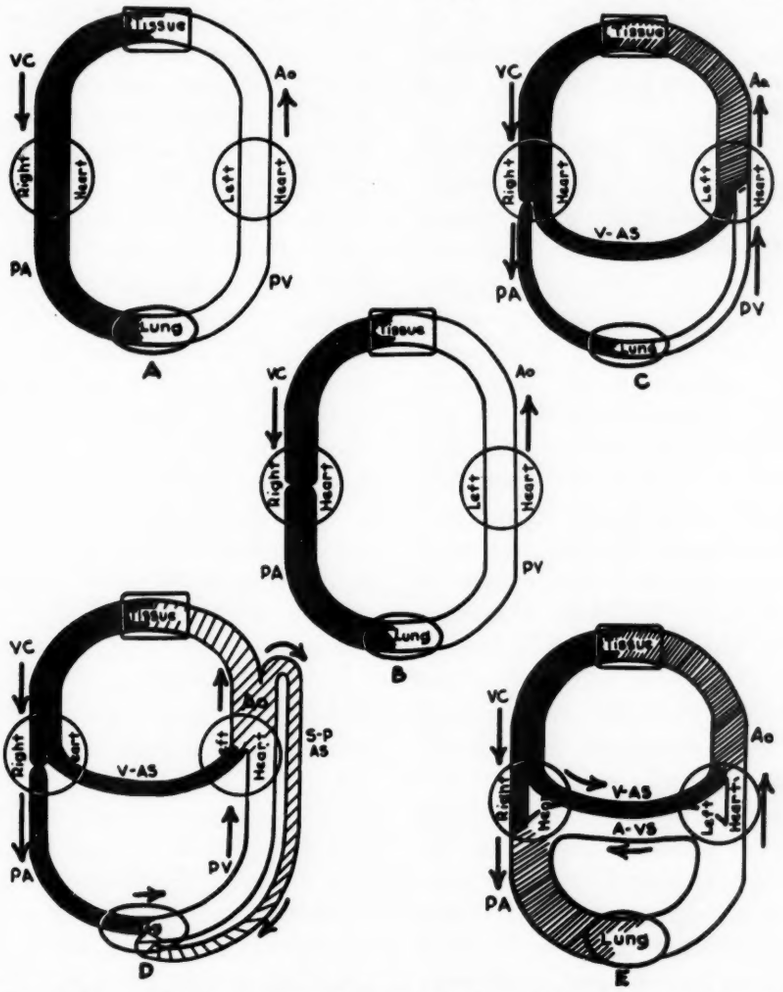


FIG. 2. Diagrammatic presentation of the path of circulation. A, normal circulation; B, circulation in pulmonary stenosis with closed septa, showing the equal volume of the systemic and pulmonary circulations; C, circulation in a case of the tetralogy of Fallot with a pure right-to-left shunt showing half of the systemic venous blood oxygenated in the lungs and half of it shunted directly into the aorta; D, similar case after a Blalock-Taussig operation in which double quantity of oxygenated blood returning from the lungs is mixed with the same quantity of venous blood as before; E, circulation in the Eisenmenger complex showing systemic venous blood entering the aorta and pulmonary venous blood entering the pulmonary artery. (Oxygenated blood is shown white, deoxygenated black, and mixed blood shaded. Arrows indicate the direction of blood flow. Abbreviations: VC, venae cavae; PA, pulmonary artery; PV, pulmonary veins; Ao, aorta; V-AS, veno-arterial shunt; A-VS, arteriovenous shunt; S-PAS, systemic-pulmonary arterial anastomosis.)

It appears that inhalation of pure oxygen raises oxygenation of the pulmonary blood by ½ to 1 volume per cent, and an additional 2 volumes per cent is dissolved in the plasma. This excess of oxygen is carried to

the left side of the heart where the mixing of oxygenated and shunted venous blood takes place and raises the saturation of the mixture over its previous level. It has been noted, however, that in cases in which anoxemia is due to shunt the maximum effect of oxygen breathing is apparent later than in other cases.[25]

Blalock and Taussig[2,3] have suggested that "inadequate circulation to the lungs" be added to the factors implicated in cyanosis by Lundsgaard and van Slyke. This was suggested in connection with their important discovery that the production of an anastomosis between a systemic artery and the pulmonary artery causes dramatic disappearance of cyanosis in cases of the tetralogy of Fallot. Their concept was that cyanosis is abolished because the operation made "circulation to the lungs adequate." The quantitative studies by Bing et al.[28] reaffirmed the pre-eminent importance of the veno-arterial shunt, but these investigators considered it only one of the factors in the production of cyanosis, stating that the "interrelationship between the veno-arterial shunt and decreased pulmonary blood flow" is responsible for anoxemia.

The suggestion that in pulmonary stenosis not enough blood reaches the lungs for oxygenation would appear to be only partially correct. The fundamental principles of hemodynamics postulate an equal output of the two ventricles under basal conditions. (Fig. 2A.) Except for momentary variations this principle holds true under all circumstances, unless abnormal communications between the two hearts are present. Thus in pulmonary stenosis with closed septa the pulmonary flow equals the systemic flow (Fig. 2B), although to maintain it a higher head of pressure in the right ventricle has to be present. In pulmonary stenosis associated with defects in the ventricular or atrial septum, or both, the pulmonary flow may be diminished by the volume of blood shunted to the left side of the heart or aorta. Thus in the case of a simple veno-arterial shunt (Fig. 2C) the volume of the blood returning to the right side of the heart from the systemic circulation divides into two parts: the portion flowing to the lungs and that shunted to the left side or aorta. The volume of the veno-arterial shunt and the pulmonary blood flow are therefore in reciprocal relationship, their sum being constant, equal to the venous return. In such an uncomplicated case, therefore, "large veno-arterial shunt" is synonymous with "small pulmonary flow" or vice versa. Since it is obvious that veno-arterial shunt is the actual cause of cyanosis, the use of the term "decreased circulation to the lungs" therefore appears illogical.

In congenital cardiac malformations of the cyanotic group the blood in the aorta has abnormally low oxygen saturation. Under normal anatomic conditions all of the blood in the aorta returns from the lungs and incompletely oxygenated arterial blood points to a faulty process of oxygenation in the lungs. In congenital malformations in which an intracardiac communication is available, incompletely saturated blood may arrive in the aorta from one or two sources, the lungs or the shunt. Thus two columns of blood having different degrees of oxygen saturation mix in the aorta, and the oxygen saturation of the arterial blood can be calculated from the following mixing equation:[13,29]

$$O_2 \text{ saturation } (\%) = \frac{\text{vol. of shunt} \times \text{its } O_2 \text{ saturation } (\%) + \text{vol. of blood returning from lungs} \times \text{its } O_2 \text{ saturation}}{\text{vol. of V-A shunt} + \text{vol. of blood returning from lungs}}$$

(Equation 1)

In cases with a pure veno-arterial shunt the volume of blood returning from the lungs involves the total pulmonary venous return. In more complicated cases in which there is a left-to-right shunt between the cardiac chambers in addition to a veno-arterial shunt, only the volume of pulmonary venous blood entering the aorta figures in the formula. Since the blood returning from the lungs is normally oxygenated, the

important variable in the formula is the quantity and saturation of venous blood entering the aorta through the shunt in relation to the total systemic flow.

This can be made clearer if one follows Lundsgaard and Van Slyke's suggestion of expressing the values in terms of oxygen unsaturation (volumes per cent of reduced hemoglobin, or oxygen capacity less oxygen content) rather than percentage saturation (ratio of oxygen content to oxygen capacity). In rewriting the equation one can simplify it by accepting that pulmonary venous blood is fully saturated (unsaturation 0 instead of the true value of 1 vol. %), which would make very little difference unless the veno-arterial shunt was very small. The following simple formula expresses this relationship:

$$\text{Arterial } O_2 \text{ unsaturation (vol. \%)} = \frac{\text{vol. of V-A shunt} \times \text{its } O_2 \text{ unsaturation}}{\text{systemic flow}}$$

(Equation 2)

From Equation 1 the volume of venous blood entering the aorta through the shunt can be easily calculated using the following equation:

$$\text{Volume V-A shunt} = \text{Systemic flow} \times \frac{O_2 \text{ content pulmonary venous blood} - O_2 \text{ content systemic arterial blood}}{O_2 \text{ content pulmonary venous blood} - O_2 \text{ content right auricular blood}}$$

(Equation 3)

Equation 3 is of practical importance since the output and all the values for oxygen contents can be determined by cardiac catheterization and thus the amount of venous blood entering the aorta calculated.

Bing, Vandam and Gray[28] introduced the concept of "diminished effective pulmonary blood flow." They define the effective pulmonary flow as the volume of blood which after passing through the right auricle eventually reaches the pulmonary epithelium. This concept is helpful by taking into consideration the fact that venous blood may reach the pulmonary epithelium not only through the pulmonary artery, but may escape oxygenation by way of the veno-arterial shunt and then reach the pulmonary epithelium through the systemic-pulmonary arterial anastomoses. The concept of cyanosis being due to "diminished effective pulmonary blood flow" is, however, also subject to criticism on two grounds: first, it presents nothing more than the simple relationship expressed in Equation 2 but does it in an indirect and unnecessarily complicated manner, and then it involves calculation of the volume of non-existing "compartment" within a blood vessel.

The simplicity with which one can express the relationship between arterial anoxemia and the veno-arterial shunt rather than to use the complicated concept of "diminished effective flow" can be shown in an example. Case 1 of Bing, Vandam and Gray[30] represents typical findings of the circulatory dynamics in the Eisenmenger complex. (Fig. 2E.) From the data reported by the authors one can calculate the volume of blood in the various segments of the circulation. Thus in the aorta the systemic flow (3.6 L.) consisted of a mixture of 1.7 L. of venous blood (saturation 68 per cent) and 1.9 L. of pulmonary venous blood (saturation 95 per cent) resulting in an oxygen saturation of the peripheral arterial blood of 83 per cent. In the pulmonary artery (pulmonary flow = 4.2 L.) there was 1.8 systemic venous blood (saturation 68 per cent) and the arteriovenous interventricular shunt bringing 2.4 L. of oxygenated pulmonary venous blood into the pulmonary artery (saturation 95 per cent). Thus the saturation of blood in the pulmonary artery was 82 per cent. It is quite obvious that the patient had arterial anoxemia and was cyanotic because the blood in the aorta and peripheral arteries contained only 53 per

cent (1.9 L.) of fully oxygenated blood from the pulmonary veins, while 47 per cent (1.7 L.) of it was venous blood shunted from the right ventricle. Yet, using the terminology of Bing et al. one would have to state that of a pulmonary flow of 4.2 L. there was only 1.8 L. of "effective pulmonary flow" which was reduced in proportion to the systemic flow and therefore the patient was anoxemic.

In conclusion, it is the opinion of the author that there is only one cause, one primary factor in the production of cyanosis in congenital heart disease, namely, the admixture of venous blood in the systemic circulation, the veno-arterial shunt. Arterial anoxemia depends entirely on how much venous blood is contained in the systemic flow and how unsaturated this blood is.

C. SECONDARY AND MODIFYING FACTORS IN THE PRODUCTION OF CYANOSIS

The preceding discussion has been limited to the primary factor, or the actual cause of cyanosis in congenital heart disease. Secondary and modifying factors, however, play an important role as they may strikingly accentuate or alleviate the intensity of cyanosis.

Peripheral Factors. Polycythemia develops as an erythropoietic response of the bone marrow to chronic anoxemia and is related to its severity. The higher content of hemoglobin accentuates cyanosis; in milder forms of anoxemia cyanosis may not be visible until the patient becomes polycythemic. The suggestion[3] that polycythemia may *per se* impair pulmonary oxygenation is not substantiated, since in polycythemia vera the arterial blood is fully saturated.

Capillary stasis develops in association with chronic anoxemia and in congenital heart disease may assume important proportion. It has been shown[31] that characteristic changes in skin capillaries are present in congenital heart disease with cyanosis, which resemble varicosities of the venous limb. These changes facilitate better utilization of oxygen but accentuate cyanosis.

Central Secondary Factors. It has been pointed out that no evidence is available that in uncomplicated cases of congenital heart disease the blood returning from the lungs is ever incompletely oxygenated. Therefore, the central factors can modify cyanosis only when (1) the ratio of veno-arterial shunt to the total systemic flow and (2) the degree of saturation of the venous blood can be affected.

These factors may be transient or permanent. The important temporary factors are exercise and heart failure.

Exercise affects the normal circulation in the following way: The cardiac output is increased, often several hundred per cent; the arteriovenous oxygen difference is increased, so that the mixed venous blood has very low oxygen saturation; the pulmonary ventilation and oxygen consumption increase. The gaseous exchange in the lungs appears to be complete in spite of the high velocity of the blood flowing through the lungs. In anoxemia due to veno-arterial shunts exercise causes a considerable accentuation of the anoxemia. There is no available evidence that during exercise pulmonary oxygenation is impaired. Lowering of the oxygen saturation during exercise is due to the following mechanism: (1) in those cases in which venous blood enters the aorta but no obstruction to the blood flow exists (e. g., the Eisenmenger complex), the increase in output presumably affects all the segments to the same degree. Thus if the output is doubled the pulmonary flow doubles, the shunt-flow doubles and the systemic flow doubles; mixing in the aorta would then be in the same proportion as at rest. However, the saturation of the venous blood which enters the aorta through the shunt is very considerably lowered, and thus the saturation of the arterial blood will be lowered in proportion (Equations 1 or 2). (2) In cases in which there is obstruction in the course of the venous blood reaching the lungs (pulmonary stenosis or tricuspid stenosis) the obstructed orifice may not be able to let more blood through during exercise than at rest. Thus in a case of the

tetralogy of Fallot (Fig. 1c) if the resting systemic flow is 4 L. of which 2 L. flow through the lungs and 2 through the shunt, and the maximum capacity of the pulmonary orifice is 2½ L. per minute, doubling of the systemic flow would lead to an increase in pulmonary flow from 2 to 2½ L., and all the rest of the returning venous blood will have to pass through the shunt (increased from 2 to 5½ L./minute). In such cases not only is the venous blood less saturated with oxygen but the proportion of the mixture in the aorta also changes so that more venous and less oxygenated blood reaches the peripheral circulation. The effect of exercise therefore is a much more profound anoxemia in cases with pulmonary stenosis than in the first group. Bing has shown another difference between the response of cyanotic patients to exercise, in that those with pulmonary stenosis show a decrease in the amount of oxygen consumed per L. of ventilation,[28,30] whereas an increased amount is consumed in those without pulmonary stenosis.

Heart failure also leads to increase in oxygen unsaturation in the cyanotic forms of congenital heart disease. With its advent two factors begin operating: (1) peripheral stasis resulting in increased desaturation of venous blood shunted into the aorta; (2) increased pressure in right cardiac chambers may affect the direction and volume of the shunt; this factor is of special importance in conditions associated with atrial septal defect. In right ventricular failure the increased right atrial pressure may accentuate a right-to-left shunt between the auricles or may even reverse the direction of a left-to-right shunt ("cyanose tardive"). In addition to these two factors specific to congenital heart disease, the usual causes of cyanosis operating in heart failure accentuate the existing cyanosis still further.

Permanent changes in the degree of anoxemia are caused by factors altering the proportion of venous and oxygenated bloods mixing in the left side of the heart or aorta. One can consider two situations: (1) factors increasing or decreasing the volume of the shunt, the pulmonary venous return being relatively constant. Such a change may be due either to altered anatomic relationship affecting the shunt or to alteration in pressures. In the first group one can visualize closure of the foramen ovale or, on the other hand, stretching of the foramen such as may occur with dilatation of the auricles. In conditions in which there is dextroposition of the aorta the degree of over-riding of the septal defect may change.[16,17] Among those factors altering the size of the shunt by pressure changes is the development of pulmonary hypertension. (2) Conditions in which the volume of the shunt is constant but the proportion of pulmonary venous blood changes are best exemplified by the development of connecting channels between systemic arteries and branches of the pulmonary artery. They increase the total flow of blood through the lungs and thereby the pulmonary venous return. Such connections include patent ductus arteriosus and dilated bronchial arteries connecting with small branches of the pulmonary artery. These connections play an important role by permitting a portion of the anoxemic arterial blood to return to the lungs for further oxygenation. Their significance is discussed in the following paragraph.

D. SURGICAL CORRECTION OF CYANOSIS

The era of surgical relief of cyanosis dates from the epoch-making work of Blalock and Taussig[2] who devised the operation connecting a large systemic artery with a pulmonary branch and noted dramatic disappearance of cyanosis. These authors advanced the concept of "inadequate circulation to the lungs" as being the cause of cyanosis, which could be reversed by reestablishment of a normal circulation at operation. It was pointed out, however, that from the physiologic standpoint it appears desirable to consider cyanosis as caused by the veno-arterial shunt and the Blalock-Taussig operation as the modifying effect of a large systemic-pulmonary arterial anastomosis upon anoxemia. This is ex-

plained diagramatically in Figure 2D. Anoxemic arterial blood is provided channels through which a portion may return to the lungs and be completely oxygenated. From the standpoint of mixing equations the operation provides an increase in the pulmonary venous return, thereby allowing more oxygenated blood to mix with the venous blood from the shunt. In the diagram, if one assumes in a hypothetical case in which before operation the systemic flow was 4 L., 2 flowing through the lungs and 2 through the shunt, after operation the systemic flow can be increased to 6 L., 4 reaching the periphery and 2 returning to the lungs. In this case the systemic venous return is constant but the pulmonary venous return doubles. Thus, before the operation 2 L. of venous blood were mixed with 2 L. of oxygenated blood, and afterward 2 L. of venous blood are mixed with 4 L. of oxygenated blood, with a corresponding increase in arterial oxygen saturation. It is possible that the Blalock-Taussig operation may invoke other, secondary changes which accentuate its beneficial effect. Thus, in the diagram it is shown that the peripheral systemic flow (aortic flow less the volume of blood shunted back to the lungs) is the same after the operation as it was before. Actually, this may not be the case since a large systemic pulmonary arterial shunt may leave *less* blood in the systemic circulation, reducing the systemic venous return and thereby the volume of the shunt. It is also conceivable that the increase in pulmonary venous return caused by the operation floods the left heart, changing the right-to-left pressure gradient and thereby reducing the shunt. These are possible ways, as yet unproven, in which the operation could not only increase the oxygenated component in the mixture but reduce the venous component. These considerations apply to resting individuals. During exercise the Blalock-Taussig operation reduces anoxemia by still another mechanism. It has been explained that in the tetralogy of Fallot the pulmonary orifice may be rigid, unable to dilate during exercise and stress. The increased output of the right ventricle then can take place only by increasing the volume of the shunt. The operation in such a case provides not only secondary channels to the lungs but adaptable channels. This can be best explained by the diagram and a hypothetical example. Before operation (Fig. 2C) if the systemic venous return doubles during exercise (from 4 to 8 L.) and the pulmonary orifice permits not more than 2 L. to pass to the lungs, the shunt would increase from 2 to 6 L. and the mixing in the aorta will be that of 2 L. oxygenated and 6 L. venous blood. After operation (Fig. 2D) the pulmonary artery flow is still 2 L. and the shunt 6 L., but the systemic flow will divide in the same proportion as before: two-thirds will enter the peripheral circulation and one-third will return to the lungs. Thus the systemic flow will be 12 L., 8 to reach the periphery and 4 to return to the lungs; in the aorta the 6 L. shunt will now mix with 6 L. of oxygenated blood, the proportion being after operation 3 to 3 instead of 3 to 1 before it. Therefore, the fall in oxygen saturation in operated patients with the tetralogy of Fallot during exercise will be predominantly due to the *quality* of venous blood whereas prior to it, in addition to qualitative changes, the *quantity* of venous blood in the aorta rose considerably in proportion to oxygenated blood. This increase in tolerance for exercise in operated patients has been noted both by clinical observation and oxymeter studies.[23]

It is obvious from the foregoing discussion that the Blalock-Taussig operation is not a specific treatment for the tetralogy of Fallot nor for pulmonary stenosis. All conditions in which venous and oxygenated blood mix before entering the systemic circulation can be benefited by increasing the proportion of oxygenated blood. Blalock[32] has shown experimentally that anoxemia caused by pulmonary arteriovenous anastomosis can be relieved by his operation. However, pulmonary stenosis associated with cyanosis will be especially benefited by the operation because (1) low pressure in the pulmonary arterial system assures good flow through

the anastomosis, and (2) there is the additional benefit of increasing tolerance to exercise.

The indications for the Blalock-Taussig operation have been aptly summarized by Burchell[33] as (1) arterial anoxemia, (2) low arterial pulmonary pressure and (3) proper oxygenation in the lungs.

It is indeed tempting to present the effects of the Blalock-Taussig operation in terms of a collateral blood supply to the lungs which restores a previously inadequate circulation. Many objections to such a concept have already been presented. In addition it should be pointed out that anastomoses between the pulmonary and systemic arteries do not represent collateral channels in the true sense. Collateral blood supply to an organ means that arterial blood takes (or is provided with) an alternate route when the main path is blocked or too narrow. In the case of pulmonary stenosis *venous* blood may be prevented from reaching the lungs if other outlets are available, but the connecting channels bring *arterial* blood to the pulmonary capillaries. While objections to Blalock and Taussig's interpretation of the significance of their operation may appear to be mere quibbling over the exact meaning of physiologic terms, in reality such concepts may lead to serious misconceptions. For example, it might be inferred erroneously that (1) the operation removes the actual cause of cyanosis and (2) it is indicated in all cases in which pulmonary stenosis is present regardless of whether or not anoxemia is found.

Other surgical attempts to attack the problem of cyanosis include Pott's[34] modification of the Blalock-Taussig operation which uses the same principle, Brock's pulmonary valvulotomy[35] and Barnett's attempt to produce anastomosis between the two circulations by obliterating the pleural cavity.[36] Brock's operation is theoretically closest to aiming at the cause of cyanosis but it is not applicable to all cases of pulmonary stenosis. Recently other operations are being studied for the relief of more complicated malformation, notably transposition of the great vessels. The feasibility of such operations has not yet been established.

E. INTERRELATIONSHIP OF SECONDARY FACTORS IN THE PRODUCTION OF CYANOSIS

The various secondary and modifying factors have profound effects on variation in the intensity of cyanosis, on its appearance and disappearance. Their interrelationship may explain some of the seemingly puzzling clinical aspects of cyanosis.

Cyanosis associated with congenital heart disease may be present since birth or it may make its appearance in infancy, childhood, adolescence or even in adult life. The intensity of cyanosis is often variable and frequently there is gradual intensification. Occasionally, on the other hand, cyanosis may become less intense or may disappear. These changes in intensity of cyanosis, its intermittence and late appearance are caused by the interplay of the following factors: Factors intensifying cyanosis, or causing latent cyanosis to become apparent: (1) possible changes in the size of the shunt (anatomic changes, altered pressure relationships), (2) secondary polycythemia, (3) capillary dilatation and stasis, (4) closure of the ductus arteriosus, (5) exercise and stress, (6) heart failure. Factors reducing cyanosis or causing transition into latent and intermittent stages: (1) closure of the foramen ovale, (2) development of systemic-pulmonary arterial anastomoses, (3) artificial systemic-pulmonary anastomosis (Blalock-Taussig operation and similar methods), (4) pulmonary valvulotomy.

F. CLINICAL SIGNIFICANCE OF CYANOSIS IN CONGENITAL HEART DISEASE

The hemodynamic effects of congenital cardiac malformations are analogous to those of acquired valvular disease. Congenital stenosis of a valvular orifice imposes strain upon a ventricle by increasing its work; intracardiac shunts increase the work of the heart by raising the output of one or both ventricles in a manner similar to valvular insufficiency. The result of these

chronic dynamic alterations is ventricular hypertrophy, dilatation and failure. In cases in which intracardiac shunts occur the rerouting of blood may lead to anoxemia and cyanosis. This, however, develops more or less accidentally and bears no relationship to the severity of the hemodynamic changes. Thus higher pressure in the left heart causes recirculation of oxygenated blood in the lesser circulation and leads to right ventricular hypertrophy. Should this relationship change and higher pressure in the right heart force venous blood to recirculate in the greater circulation, then in addition to the hemodynamic effects of the shunt anoxemia with its serious physiologic derangement develops.

Thus cyanosis may develop entirely independently of cardiac strain, enlargement of the heart and cardiac failure. It therefore bears little relationship to the over-all prognosis of a case except when extreme, as it may then set in operation a serious chain of events which may cause death even in the absence of circulatory embarrassment. Patients with lowered oxygen saturation of the arterial blood develop some adaptive changes, such as polycythemia, capillary dilatation permitting better utilization of oxygen and a lowered basal metabolism,[28] which perhaps means tissue adaptation to lower oxygen tension. While chronic anoxemia may be compatible with relative comfort and even fair tolerance for exertion, during unusual stress or an intercurrent illness the patient's reserve may disappear so that a relatively minor illness may prove fatal. Some of the adaptive phenomena may also overshoot the mark of physiologic usefulness and aggravate instead of alleviate the illness. This is exemplified by polycythemia, which on one hand permits the blood to carry more oxygen at a given tension and on the other hand may become a serious hazard by increasing the viscosity of blood and predisposing to thrombotic phenomena.

It is important therefore in considering surgical treatment of cyanosis to appreciate the fact that the operation offers only symptomatic, partial relief and may impose an additional serious burden upon the circulatory dynamics. Only careful balancing of the desirability of correction of anoxemia against the possible harmful effect of a large systemic pulmonary shunt upon cardiodynamics can lead to the proper selection of cases for surgical treatment.

II. CYANOSIS DUE TO PULMONARY FACTORS

Lowered Barometric Pressure. Lowered barometric pressure produces low oxygen tension in the pulmonary alveoli and incomplete oxygen saturation of the arterial blood without involving any pathologic process. Inhabitants of high altitude areas have chronic arterial anoxemia and as a rule develop secondary polycythemia, which disappears upon transfer to sea level. Above 10,000 feet elevation anoxemia is severe enough so that many subjects may appear cyanotic, particularly on exertion. At 17,000 feet cyanosis is usually present at rest.[37] Polycythemia in patients living at high altitudes is an adaptive phenomenon permitting them to be more active. Hurtado et al.[38] and Merino et al.[39] studied the relationship between the anoxemic stimulus and the development of polycythemia. They showed a definite correlation between the arterial oxygen saturation and the hematopoietic activity of the bone marrow. Hurtado et al.[38] showed also summation of factors, for instance miners with silicosis living at high altitudes develop a greater degree of cyanosis with polycythemia and clubbing than develops either with low barometric pressure or silicosis alone. Another factor which appears to be adaptive is the presence of emphysema, which was found by Talbott and Dill[35] in apparently healthy individuals living at high altitudes. This is associated with an increased vital capacity.

Chronic Mountain Sickness.[40,41] Some inhabitants of high altitude areas are reported as developing the syndrome of chronic mountain sickness, which is a marked accentuation of the polycythemia with clubbing, severe cyanosis and, in many cases, evidence of pulmonary hypertension with right-sided heart strain and failure. This

condition was studied by Monge[40] who thought it to be due to a loss of tolerance to lowered barometric pressure, and considered the exaggerated polycythemia an effort to compensate for failure of other adaptive phenomena. Such cases were also reported by Talbott and Dill[38] and by Hurtado.[41] The latter author noted that in such patients the arterial oxygen saturation was lower than in other inhabitants of these localities, and suggested that polycythemia represents the usual response to more severe anoxia rather than an unusual response to the same stimulus. Hurtado suggested that additional pulmonary factors may develop in inhabitants of high altitude areas which accentuate their anoxemia.

It appears then that some inhabitants of high altitude regions develop severe cyanosis with high degree of polycythemia and clubbing and suffer from symptoms of anoxemia complicated by right-sided heart disease which disappear on transfer to lower altitude. In view of Hurtado's findings one wonders whether there is justification for the isolation of this symptom complex as a clinical syndrome. It seems not unreasonable to suppose that these are simply cases of bronchitis, emphysema, pulmonary fibrosis developing in inhabitants on high altitudes, and that these patients improve strikingly when one cause of anoxemia (high altitude) is eliminated.

Pulmonary Disease Associated with Chronic Cyanosis. Chronic pulmonary emphysema is an important cause of arterial anoxemia. The fact that cyanosis either at rest or on exertion occurs frequently in pulmonary emphysema is well known. Older studies[42,45] have shown that there is a relationship between the degree of emphysema and arterial oxygen saturation. Recently the subject has been reinvestigated by Baldwin et al.[46] and the various physiologic measurements were used as means of classifying emphysema. It was shown that in milder forms of emphysema loss of elasticity of the lungs[47] and poor pulmonary ventilation are the most important features. In such cases arterial oxygen saturation is normal both at rest and during exercise, as emphysema appears to be compensated by hyperventilation. In more severe cases, in addition to ventilatory insufficiency there is also alveolorespiratory insufficiency, evidenced by disturbance in air distribution through the alveoli. In such cases anoxemia becomes apparent at first on exertion, in more advanced cases also at rest. In severe cases cyanosis may be striking and secondary polycythemia with clubbing is common. In such severe cases pulmonary hypertension develops and leads to right ventricular hypertrophy and failure. In the series studied by Baldwin et al.[46] it was noted that polycythemia was usually not present unless chronic cardiac failure was present in addition to emphysema.

Pulmonary fibrosis is also frequently associated with chronic anoxemia and cyanosis. Most students of the subject, however, are in agreement that pulmonary fibrosis is a less important factor in the production of anoxemia than emphysema.[48,49] The factor responsible for anoxemia in pulmonary fibrosis is alveolar hypoventilation, which leads to a mild degree of anoxemia unless chronic pulmonary emphysema is also present (the combination of the two is very common). In rare cases there is, in addition, actual thickening of the alveolar membrane. Such changes have been found in rare cases of chronic pulmonary fibrosis by Baldwin et al.[49] and were described in more acute form in Hamman and Rich's "acute interstitial fibrosis"[50] and the recently emphasized beryllium poisoning.[51]

Association of Cyanosis with Pulmonary Vascular Disease. In the mind of the clinician cyanosis is often associated with disorders of the pulmonary circulation. "Cor pulmonale," "Ayerza's disease" and "pulmonary vascular sclerosis" are clinical and pathologic terms in which cyanosis is thought to be an important sign.

Physiologically, pulmonary circulatory disease is characterized by pulmonary arterial hypertension; anatomically, pulmonary arterial or arteriolar sclerosis varies from mere plaques in the large branches to diffuse severe obliterative arteriolar changes.

One may ask the question: In what way do pulmonary arterial hypertension and pulmonary arterial disease lead to impaired oxygen exchange in the lungs and anoxemia? In order to attempt to answer this question it is necessary to review the various causes of pulmonary vascular disease and establish the incidence of cyanosis, clubbing and polycythemia in association with them.

The commonest cause of "cor pulmonale" with pulmonary vascular sclerosis is chronic pulmonary emphysema and fibrosis. As already pointed out, in both conditions cyanosis and anoxemia are due to disorders of the ventilatory and respiratory functions of the lungs.

If circulatory changes in the lungs *per se* can cause cyanosis, anoxemia should be demonstrated in those conditions in which pulmonary arterial disease is present without impairment of the pulmonary functions. Such conditions belong in two groups: primary vascular disease and pulmonary hypertension associated with some cardiac disorders.

Primary pulmonary vascular sclerosis is a very rare clinical and pathologic entity. Brenner,[57] setting rigid criteria, selected out of a group of over 100 cases of severe pulmonary arteriosclerosis reported in the literature only fifteen in which no associated disease of the lungs, heart and pleura were reported, so that these could be accepted as "primary." Brill and Krygier[53] supplemented this series with five more cases. These twenty cases were reviewed with reference to polycythemia and cyanosis. In three cases, only the pathologic description was reported; in four others clinical data were incomplete. Of the thirteen cases in which clinical information was available all patients had chronic severe heart failure during the time they were observed. Cyanosis was reported as mild in five cases, moderate in five, severe in two and absent in one. Blood studies were available in four cases, two of which[53,54] showed polycythemia. Clubbing was not mentioned in any of the thirteen cases. Considering the fact that heart failure by itself is a factor in the production of cyanosis, one can conclude that long-standing severe cyanosis is not a constant finding in severe primary pulmonary endarteritis.

"Ayerza's disease" is a term which has acquired a considerable popularity in the medical literature. Originally described by Ayerza and his pupil Arrillaga[55] to signify severe degree of cyanosis and polycythemia ("black cardiac") associated with pulmonary disease presumed to be on a syphilitic basis, it has been used by various authors to signify a variety of conditions. Brenner[52] reviewed the subject critically and decided that there is no specific clinical and pathologic picture of "Ayerza's disease." Most cases have been reported in the South American literature but even among South American workers there is no agreement as to the exact nature of this syndrome.[55,57] It is noteworthy, however, that in all cases reported as "Ayerza's disease" pulmonary emphysema or fibrosis was present. Inasmuch as the basic feature of this syndrome is severe cyanosis with polycythemia and no common underlying factor is claimed, this term should be abandoned since all it appears to convey is severe anoxemia and cyanosis due to any pulmonary factor; it is not a disease entity.

Cardiovascular disease causing pulmonary hypertension (with the exclusion of cardiac failure): This group of conditions includes congenital and acquired cardiac disorders: mitral stenosis, atrial septal defect, ventricular septal defect, the Eisenmenger complex and patent ductus arteriosus. The pulmonary artery pressure in them varies from normal values to extreme hypertension. Sclerotic changes in the pulmonary artery and its branches are very common, in some of these conditions even characteristic. Welch and Kinney[58] recently investigated the occurrence of these vascular changes in congenital cardiovascular malformations and found that pulmonary arteriolar changes are much more prominent when mitral stenosis is superimposed upon them. They did show, however, the fairly constant occurrence of such vascular changes in lesions associated with a left-to-right blood

shunt, and their severity appeared to have been related to the increase in vascular flow.

Persistent cyanosis does not occur frequently in mitral stenosis and in most congenital malformations with a left-to-right shunt. Cyanosis in mitral stenosis appears to be mostly peripheral in origin[59,60] and objective signs of chronic anoxemia, clubbing and polycythemia do not occur in uncomplicated mitral stenosis. This fact deserves special emphasis since mitral stenosis is the commonest and most important cause of chronic pulmonary hypertension and pulmonary vascular sclerosis and these vascular changes may be of such magnitude that they have been compared to systemic arteriolar changes in malignant hypertension.[61] Atrial septal defect is another condition often associated with pulmonary hypertension and vascular changes, and yet chronic cyanosis appears to be present in only 8 per cent of cases, and is best explained on the basis of an intracardiac shunt.[18] Veno-arterial shunt offers the best explanation for the cyanosis associated with the Eisenmenger complex and the rare instances of cyanosis in ventricular septal defects and patent ductus. The recently reported severe arteriolar changes in cases of patency of the ductus arteriosus associated with coarctation of the aorta are apparently not the cause of cyanosis in this syndrome, as cyanosis is noted in the lower part of the body and occasionally the left arm,[20] thus being related to the flow of venous blood through the ductus to the aorta below the coarctation.

All the preceding considerations force one to conclude that cyanosis is *not* a constant finding in pulmonary vascular disease, and when present appears to be in no causal relationship to it. This conclusion finds confirmation in the study of Weber[62] who approached the problem from another angle by collecting cases of secondary polycythemia (erythremia). In the group not associated with congenital heart disease pulmonary disease was uniformly present. In six such cases brought to autopsy chronic pulmonary emphysema was present in all, and in addition extensive pleural adhesions were found in four of them. On the other hand, pulmonary vascular changes were not striking in these cases and right ventricular hypertrophy (indicative of pulmonary hypertension) was noted prominently in only two cases.

Cyanosis Due to Cardiac Failure. Cyanosis associated with cardiac failure appears to be due to a combination of pulmonary and peripheral factors. The exact contribution of the two factors in the production of cyanosis has not been established. Intermittent cyanosis and cyanosis appearing during attacks of dyspnea are unquestionably central in origin. It is generally accepted that not only in acute pulmonary edema but also in milder forms of paroxysmal dyspnea edema of the alveolar membrane may develop and interfere with gaseous exchange.

Chronic cyanosis appearing at rest and not associated with any apparent distress is not uncommon in congestive cardiac failure. Studies of arterial oxygen saturation in comfortably resting patients are not very numerous but they have established the fact that arterial anoxemia may be absent and that, if present, the degree bears no relationship to the severity of cardiac failure.[59,63–65] Arterial anoxemia, however, has been demonstrated quite frequently in sufficient severity to cause visible cyanosis. The cause of anoxemia has not been definitely established. One can only speculate about the various possible mechanisms: chronic thickening of the alveolar membrane; pulmonary congestion leading to perfusion of poorly ventilated alveoli; loss of elasticity of the lungs from pulmonary congestion or the development of pulmonary emphysema. The frequency of emphysema has been pointed out by Christie and Meakins[65] and it is possible that the presence of emphysema in cardiac failure is needed for the production of arterial anoxemia. The subject of cyanosis in cardiac failure appears to be in need of further investigation.

Peripheral cyanosis due to capillary

stasis finds support in the persistent finding of slowing of the circulation in cardiac failure. It unquestionably plays a very important part in the development of chronic cyanosis. The fact that the usual secondary sequelae of arterial anoxemia, polycythemia and clubbing of digits, appear very seldom in association with congestive heart failure suggests that stagnant cyanosis may be a more important part of congestive failure than anoxemic cyanosis, and that arterial anoxemia, when present, may be of lesser severity, persistence and duration than in other conditions.

Cyanosis Due to Pulmonary Arteriovenous Fistula. Within the past ten years several cases of localized cavernous hemangioma of the lungs have been reported. This condition is of special physiologic interest since the hemangioma acts as an arteriovenous fistula, permitting venous blood to enter directly from the pulmonary artery to the pulmonary vein (intrapulmonary veno-arterial shunt). Such cases were recently analyzed by Burchell et al.[66] and Baker and Trounce.[67] The patients have an appearance similar to those with congenital heart disease of the cyanotic group, and cyanosis, polycythemia and clubbing may reach very considerable proportions (11 million erythrocytes and 138 per cent hemoglobin in one such case). It is most interesting to note that very large quantities of blood are drawn into these hemangiomas. In Baker and Trounce's case 1, in which catheter studies were performed, it was calculated that the pulmonary arterial flow was 12 L. of which 9.5 L. were shunted into the pulmonary vein in the hemangioma, while only 2.5 L. reached the pulmonary capillaries. Thus in these patients the circulation is that of a large veno-arterial shunt situated outside the heart. As expected, arterial oxygen saturation is very low, values of 60 to 75 per cent being recorded in the majority of cases.

The most striking feature of this syndrome is the fact that surgical removal of the hemangioma is feasible and thus the cyanosis can be cured in the true sense. As expected, in successfully treated cases oxygen saturation is not merely higher than before operation, as in surgically treated cases of tetralogy of Fallot, but brought all the way to normal levels and polycythemia and clubbing disappear.

Physiologic Considerations of the Pulmonary Factors. Lowered oxygen saturation of the blood returning from the lungs may be due to one of four mechanisms: (1) lowered oxygen tension in the alveolar air in a significant number of perfused alveoli; (2) change in the alveolar membrane interfering with gaseous exchange; (3) blood perfusing unaerated sections of the lungs and (4) direct connections between branches of the pulmonary artery and veins. The important clinical conditions associated with pulmonary vein anoxemia were discussed above, and it is seen that in some of them a single factor, in others a combination of factors is responsible for the anoxemia.

Lowered alveolar oxygen tension is the most important factor in the production of chronic cyanosis. It may be due to extrinsic causes (lowered barometric pressure) or to pulmonary disease. In chronic pulmonary emphysema lowered alveolar oxygen tension is due in part to ventilatory insufficiency and in part to respiratory insufficiency with alveolar hypoventilation.

Impaired diffusion through altered alveolar membranes is exemplified as a temporary condition in pulmonary edema, and as a chronic state in some forms of pulmonary fibrosis and beryllium poisoning.

The significance of unaerated sections of the lungs in the production of anoxemia has recently been reinvestigated.[68] An effective mechanism for redistribution of blood shunted from the unaerated to aerated sections of the lungs was demonstrated so that this factor appears to play a minor part in the production of anoxemia.

The problem of pulmonary arteriovenous connections has been presented in connection with hemangioma of the lungs where it appears in pure form. Recently, Prinzmetal et al.[69] demonstrated the existence of arteriovenous pulmonary connections of significant caliber in normal animals. Their physiologic

significance in health and disease is as yet unknown.

The important problem of the relationship between pulmonary hypertension, pulmonary vascular disease and arterial anoxemia has been discussed in its essential points. It was shown that in cases in which prominent anoxemia is present in combination with either pulmonary hypertension and vascular sclerosis, or both, some form of pulmonary insufficiency or a veno-arterial shunt can almost always be demonstrated. In other cases anoxemia is usually absent. Theoretically, the connection between pulmonary hypertension and arteriolar obstruction on one hand, and impaired pulmonary gas exchange on the other, is not at all clear. One can repeat the argument used in the discussion of pure pulmonary stenosis, that obstruction to flow along the course of the pulmonary artery does not cause anoxemia *per se* since all the blood has to flow through the lungs regardless of the obstruction. Sclerotic and obliterative changes affecting even the smallest caliber vessels would not be likely to extend to the capillaries and the alveolar membrane; such changes have never been demonstrated. Whether sclerotic vascular changes could alter the elasticity of the lungs, leading to hypoventilation, is a matter of speculation as no studies of respiratory function are available in cases not associated with primary pulmonary disease. One could also entertain the possibility that the physiologic arteriovenous connections may acquire an important function under certain conditions providing a bypass for venous blood into the pulmonary veins.

One can thus speculate on the mode of action by which pulmonary vascular disease could bring about arterial anoxemia. However, present knowledge indicates that anoxemia and cyanosis on the one hand and pulmonary hypertension and vascular sclerosis on the other are both caused by chronic pulmonary disease and are in no other relation to each other. Thus emphysema and fibrosis through pulmonary insufficiency lead to anoxemia and cyanosis; and through reduction of the capacity of the vascular bed, or some other mechanism, cause pulmonary hypertension which in turn leads to pulmonary arteriolar sclerosis, right ventricular hypertrophy and failure ("cor pulmonale").

III. CYANOSIS DUE TO STAGNANT ANOXEMIA

Cyanosis due to capillary stasis is the commonest form of cyanosis. It accounts for all forms of localized cyanosis due to disturbance of venous drainage or arterial supply. It includes constitutional acrocyanosis of some individuals and cyanosis due to low temperatures.

Generalized stasis may occur in cardiac failure and in states associated with high venous pressure (constrictive pericarditis, tricuspid valve disease) and plays an important role in the production of cyanosis in cardiac failure, as already indicated.

In addition, capillary stasis is an important secondary factor in all forms of arterial anoxemia, especially that associated with congenital heart disease.

IV. CYANOSIS DUE TO POLYCYTHEMIA

Polycythemia is an important factor in the production of cyanosis in that the physiologic unsaturation of capillary blood in the presence of a high content of hemoglobin often reaches values above the threshold of visible cyanosis. Thus polycythemia developing in response to anoxemia contributes to the cyanotic color of the anoxemic patient.

However, the importance of polycythemia as a *primary* factor is limited to polycythemia vera. It has been established beyond doubt that polycythemia vera bears no relationship to anoxemia[70,73] and that the arterial oxygen saturation is normal. It is thus sharply differentiated from secondary polycythemia ("erythrosis") in which there is lowered arterial oxygen saturation. In patients with polycythemia vera of severe degree there may be a cyanotic tinge to the skin. In others, cyanosis may become visible on exertion. It is probable that a contributory factor in the production of cyanosis in

polycythemia vera is capillary dilatation (stagnant cyanosis) due to increase in blood volume (plethora).

REFERENCES

1. Lundsgaard, C. and Van Slyke, D. D. Cyanosis. *Medicine*, 2: 1, 1923.
2. Blalock, A. and Taussig, H. B. The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. *J. A. M. A.*, 128: 189, 1945.
3. Taussig, H. B. and Blalock, A. Observations on the volume of the pulmonary circulation and its importance in the production of cyanosis and polycythemia. *Am. Heart J.*, 33: 413, 1947.
4. Lungsgaard, C. Studies on cyanosis. I. Primary causes of cyanosis. *J. Exper. Med.*, 30: 259, 1919.
5. Lundsgaard, C. Studies on cyanosis. II. Secondary causes of cyanosis. *J. Exper. Med.*, 30: 271, 1919.
6. Comroe, J. H. and Botelho, S. The unreliability of cyanosis in the recognition of arterial anoxemia. *Am. J. M. Sc.*, 214: 1, 1947.
7. Garland, L. H. On the scientific evaluation of diagnostic procedures. *Radiology*, 52: 309, 1949.
8. Lewis, T. Diseases of the Heart. London, 1933. Macmillan and Co.
9. Baldwin, E. de F., Cournand, A. and Richards, D. W. Pulmonary insufficiency. I. Physiological classification; clinical methods of analysis; standard values in normal subjects. *Medicine*, 27: 243, 1948.
10. Abbott, M. E. Congenital Heart Disease. Nelson's Loose-leaf Medicine 4: 207–321, 1932.
11. Taussig, H. B. Congenital Malformations of the Heart. New York, 1947. Commonwealth Fund.
12. Glendy, M. M., Glendy, R. E. and White, P. D. Cor biatriatum triloculare: case report. *Am. Heart J.*, 28: 395, 1944.
13. Selzer, A. and Carnes, W. H. The pathogenesis of cyanosis associated with pulmonary stenosis. To be published.
14. Selzer, A., Carnes, W. H., Noble, C. A., Jr., Higgins, W. H., Jr. and Holmes, R. O. The syndrome of pulmonary stenosis with patent foramen ovale. *Am. J. Med.*, 6: 3, 1949.
15. Burwell, C. S. Studies of the circulation in congenital affections of the heart and their application to some problems of heart disease. *Tr. & Stud., Coll. Physicians, Philadelphia*, 10: 82, 1942.
16. Selzer, A. and Laquer, G. L. The Eisenmenger complex and its relation to the uncomplicated defect of the ventricular septum. *Arch. Int. Med.*, in press.
17. Selzer, A. Defect of the ventricular septum. Summary of twelve cases and review of the literature. *Arch. Int. Med.*, 84: 798, 1949.
18. Selzer, A. and Lewis, A. E. The occurrence of chronic cyanosis in atrial septal defect. *Am. J. M. Sc.*, 218: 516, 1949.
19. Douglas, J. M., Burchell, H. B., Edwards, J. E., Dry, T. J. and Parker, R. L. Systemic right ventricle in patent ductus arteriosus: report of a case with obstructive pulmonary vascular lesions. *Proc. Staff Meet., Mayo Clin.*, 22: 413, 1947.
20. Edwards, J. E., Douglas, J. M., Burchell, H. B. and Christensen, N. A. Pathology of the intrapulmonary arteries and arterioles in coarctation of the aorta associated with patent ductus arteriosus. *Am. Heart J.*, 38: 205, 1949.
21. Handelsman, J. C., Bing, R. J., Campbell, J. A. and Griswold, H. E. Physiological studies in congenital heart disease. V. The circulation in patients with isolated septal defects. *Bull. Johns Hopkins Hosp.*, 82: 615, 1948.
22. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sagerson, R. P. and Evans, J. M. Studies of congenital heart disease. II. The pressure and oxygen contents of blood in the right auricle, right ventricle and pulmonary artery in control patients with observations on the oxygen saturation and source of pulmonary "capillary" blood. *J. Clin. Investigation*, 26: 554, 1947.
23. Bing, R. J., Vandam, L. D. and Gray, F. D. Physiological studies in congenital heart disease. I. Procedures. *Bull. Johns Hopkins Hosp.*, 80: 107, 1947.
24. Fowler, W. J. and Comroe, J. H. The rate of increase of arterial saturation following inspiration of 100% oxygen. *Federation Proc.*, 6: 104, 1947.
25. Gullickson, G., Elam., J. O., Hammond, M., Paine, J. R. and Varco, R. L. Oxygenation studies in congenital pulmonary stenosis. *Am. Heart J.*, 35: 940, 1948.
26. Montgomery, G. E., Geraci, J. E., Parker, R. L. and Wood, E. H. The arterial oxygen saturation in cyanotic types in congenital heart disease. *Proc. Staff Meet., Mayo Clin.*, 23: 169, 1948.
27. Burchell, H. B. The application of oxymetry and cardiac catheterization in the diagnosis of congenital heart disease. *J. Iowa M. Soc.*, 38: 364, 1948.
28. Bing, R. J., Vandam, L. D., Gray, F. D., Jr. Physiological studies in congenital heart disease. II. Results of preoperative studies in patients with tetralogy of Fallot. *Bull. Johns Hopkins Hosp.*, 80: 121, 1947.
29. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. E. and Evans, J. M. Studies in congenital heart disease. I. Techniques of venous catheterization as a diagnostic procedure. *J. Clin. Investigation*, 26: 547, 1947.
30. Bing, R. J., Vandam, L. D. and Gray, F. D., Jr. Physiological studies in congenital heart disease. III. Results obtained in 5 cases of Eisenmenger's complex. *Bull. Johns Hopkins Hosp.*, 80: 323, 1947.
31. Redisch, W. and Rösler, H. Beiträge zur Lehre von den angeborenen Herzfehlern: Kapillarstudien. *Wien. Arch. f. inn. Med.*, 16: 463, 1929.
32. Blalock, A. Effect of an artificial ductus arteriosus on experimental cyanosis and anoxemia. *Arch. Surg.*, 52: 247, 1946.
33. Burchell, H. B. Congenital heart disease: physiologic considerations. *Postgrad. Med.*, 3: 321, 1948.
34. Potts, W. J., Smith, S. and Gibson, S. Anastomosis of the aorta to a pulmonary artery. *J. A. M. A.*, 132: 627, 1946.
35. Brock, R. C. Pulmonary valvulotomy for the relief of congenital pulmonary stenosis. *Brit. M. J.*, 1: 1121, 1948.

36. Barnett, N. R. and Dailey, R. Increasing lung blood supply in congenital heart disease. *Brit. M. J.*, 1: 699, 1949.
37. Talbott, J. H. and Dill, D. B. Clinical observations at high altitude. Observations on six healthy persons living at 17,000 feet and a report of one case of chronic mountain sickness. *Am. J. M. Sc.*, 192: 626, 1936.
38. Hurtado, A., Merino, C. and Delgado, E. Influence of anoxemia on the hematopoietic activity. *Arch. Int. Med.*, 74: 284, 1945.
39. Merino, C. F. and Reynafarje, C. Bone marrow studies in polycythemia of high altitude. *J. Lab. & Clin. Med.*, 34: 637, 1949.
40. Monge, C. High altitude disease. *Arch. Int. Med.*, 59: 32, 1937.
41. Hurtado, A. Chronic mountain sickness. *J. A. M. A.*, 120: 1278, 1942.
42. Kaltreider, N. L., Hurtado, A. and Brooks, W. W. Study of the blood in chronic respiratory diseases with special reference to the volume of blood. *J. Clin. Investigation*, 13: 999, 1934.
43. Hurtado, A., Kaltreider, N. L., Fray, W. W., Brooks, W. D. W. and McCann, W. S. Studies of total pulmonary capacity and its subdivision. VI. Observations in cases of obstructive emphysema. *J. Clin. Investigation*, 13: 1027, 1934.
44. Knipping, H. W., Lewis, W. and Montcrieff, A. Ueber die Dyspnoe. *Beitr. z. Klin. d. Tuberk.*, 79: 1, 1932.
45. Knipping, H. W. Dyspnoe. *Beitr. z. Klin. d. Tuberk.*, 82: 133, 1933.
46. Baldwin, E. de F., Cournand, A. and Richards, D. W. Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 201, 1949.
47. Christie, R. V. The elastic properties of the emphysematous lung and their clinical significance. *J. Clin. Investigation*, 13: 295, 1934.
48. Hurtado, A., Kaltreider, N. L. and McCann, W. J. Studies of total pulmonary capacity and its subdivision. IX. Relationship to the oxygen saturation and carbon dioxide content of the arterial blood. *J. Clin. Investigation*, 14: 94, 1935.
49. Baldwin, E. de F., Cournand, A. and Richards, D. W. Pulmonary insufficiency. II. A study of 39 cases of pulmonary fibrosis. *Medicine*, 28: 1, 1949.
50. Hamman, L. and Rich, A. R. Acute diffuse interstitial fibrosis of the lungs. *Bull. Johns Hopkins Hosp.*, 74: 177, 1944.
51. Hardy, H. L. and Tabershaw, I. R. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. *J. Indust. Hyg. & Toxicol.*, 28: 197, 1946.
52. Brenner, O. Pathology of the vessels of the pulmonary circulation. *Arch. Int. Med.*, 56: 211, 457, 724, 976, 1189, 1935.
53. Brill, I. C. and Krygier, J. J. Primary pulmonary vascular sclerosis. *Arch. Int. Med.*, 68: 560, 1941.
54. McCallum, W. G. Obliterative pulmonary arteriosclerosis. *Bull. Johns Hopkins Hosp.*, 49: 37, 1931.
55. Arrilaga, F. C. La Arteritis Pulmonar y su Cuadro Clinico. Buenos Aires, 1925. El Ateneo.
56. Ayerza, L., Solari, L. A. and Berconsky, J. Cyanose par hypoventilation alveolaire chez un cardiaque noir d'Ayerza. *Arch. d. mal. du Coeur.*, 24: 209, 1931.
57. Cossio, P. and Berconsky, I. Syndrome d'hypoventilation alveolaire. *Rev. sud-am. de méd. et de chir.*, 3: 705, 1932.
58. Welch, K. J. and Kinney, T. D. The effect of patent ductus arteriosus and of interauricular and interventricular septal defects on the development of pulmonary vascular lesions. *Am. J. Path.*, 24: 729, 1948.
59. Fraser, F. R. Goulstonian lectures on cardiac dyspnea. *Lancet*, 1: 529, 589, 643, 1927.
60. Cossio, P. and Berconsky, J. The cyanosis in mitral stenosis. *Am. Heart J.*, 17, 1, 1939.
61. Parker, F., Jr. and Weiss, S. The nature and significance of the structural changes in the lungs in mitral stenosis. *Am. J. Path.*, 12: 573, 1936.
62. Weber, F. P. The prognostic significance of secondary polycythemia in cardio-pulmonary cases. *Proc. Roy. Soc. Med.*, 6: 83, 1913.
63. Barach, A. L. and Woodwell, M. N. Studies in oxygen therapy with determination of the blood cases. I. In cardiac insufficiency and related conditions. *Arch. Int. Med.*, 28: 367, 1921.
64. Schoen, R. and Derra, E. Untersuchungen ueber die Bedeutung der Zyanose als klinisches Symptom. *Deutsches Arch. f. klin. Med.*, 168: 52, 1930.
65. Christie, R. V. and Meakins, J. C. The intrapleural pressure in congestive heart failure and its clinical significance. *J. Clin. Investigation*, 13: 323, 1934.
66. Burchell, H. B. and Clagett, O. T. The clinical syndrome associated with pulmonary arteriovenous fistulas including a case report of a surgical cure. *Am. Heart J.*, 34: 151, 1947.
67. Baker, C. and Trounce, J. R. Arteriovenous aneurysm of the lung. *Brit. Heart J.*, 9: 109, 1949.
68. Cournand, A. Recent observations on the dynamics of the pulmonary circulation. *Bull. New York Acad. Med.*, 23: 27, 1947.
69. Prinzmetal, M., Ornitz, E. M., Jr., Simkin, B. and Bergman, H. C. Arteriovenous anastomosis in the liver, spleen, and lungs. *Am. J. Physiol.*, 152: 48, 1948.
70. Barach, A. L. and McAlpin, K. R. Negative results of oxygen therapy in polycythemia vera. *Am. J. M. Sc.*, 185: 178, 1933.
71. Hitzenberger, K. Die Sauerstoffsaettigung des arteriellen Blutes bei Polycythaemien. *Ztschr. f. klin. Med.*, 126: 495, 1934.
72. Altschule, M. D., Volk, M. C. and Henstell, H. Cardiac and respiratory function at rest in patients with uncomplicated polycythemia vera. *Am. J. M. Sc.*, 200: 478, 1940.
73. Wasserman, L. R., Dobson, R. L. and Lawrence, J. H. Blood oxygen studies in patients with polycythemia and in normal subjects. *J. Clin. Investigation*, 28: 60, 1949

Seminars on Pulmonary Physiology

Interpretation of Commonly Used Pulmonary Function Tests*

JULIUS H. COMROE, JR., M.D.
Philadelphia, Pennsylvania

WITHIN the past decade there has been increasing interest in the use of physiologic tests for the qualitative and quantitative evaluation of pulmonary function in patients with abnormalities of the cardiopulmonary system. The list of such tests, including variations upon basic procedures, has become large and the individual tests have become increasingly complex. This review will be limited to the more commonly used tests which can be employed without unusual or expensive equipment. Further, it will be limited almost entirely to the *interpretation* of these. A complete account of the methods themselves has been published within the past year[12] and should be consulted for details.

Pulmonary function tests have been accepted quickly and eagerly by the medical profession. In general, however, clinicians expect more of these tests than they can provide, this in part because the limitations of these studies are not usually stressed. What are these limitations? First, physiologic studies do not provide anatomic, pathologic or microbiologic diagnoses but only an analysis of functional disturbances. For example, function tests may reveal the existence of a venous-arterial shunt but in themselves cannot locate it geographically as being intracardiac or intrapulmonic. Again, physiologic tests may indicate that there is impairment of diffusion across the alveolar capillary membrane but cannot differentiate interstitial edema from intra-alveolar edema, nor can they determine whether the intra-alveolar fluid is exudate or transudate. Second, they do not reveal alterations in all types of pulmonary disease but only when the lesion disturbs function and disturbs it sufficiently that present tests can recognize with certainty the deviation from normal values. In general, they cannot detect slight reduction in functioning pulmonary tissue or small areas in the lungs that receive neither ventilation nor circulation. Physiologic tests will be normal in the presence of lesions such as fibrotic tuberculous cavities, cysts or carcinomatous nodules unless these lesions occupy so much space that they reduce the lung volume well below normal limits or are so strategically located as to disturb pulmonary function. Thus pulmonary function studies will not tell *where* the lesion is, *what* the lesion is or even *that a lesion exists*, if it does not interfere with the function of the lung. These examples serve to emphasize that these tests do not supplant radiologic, bacteriologic and pathologic studies. Interestingly enough, within the past several months the Sub-Committee on Pulmonary Function Tests of the American Trudeau Society listed the minimal requirements as: "careful analysis of the history, physical examination, a fluoroscopic examination which attempts to evaluate the magnitude, speed and distribution of pulmonary ventilation, inspiratory and expiratory chest x-rays and"—only one procedure usually categorized as a pulmonary function test—"determination of the maximal breathing capacity."[36]

What may be accomplished, then, by the

* From the University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.

use of pulmonary function studies? Certainly they can provide an *objective* appraisal of pulmonary disability which will be useful in evaluating cases involving pulmonary disease; some patients with extensive radiologic shadows may have little disturbance in function while others with relatively little radiologic evidence of disease may have true pulmonary disability.[56] They are useful in ruling out pulmonary disease in nonorganic types of dyspnea associated with hysteria or neurocirculatory asthenia. They often furnish a quantitative measure of pulmonary function which can aid in the evaluation of candidates for permanent forms of collapse therapy or surgical removal of lung tissue, both so far as immediate risk and ultimate useful existence are concerned. They enable the clinician to follow objectively certain aspects of the course of pulmonary disease and to evaluate therapy, medical or surgical. They often aid considerably in differentiating many types of cardiac disease from pulmonary disease and in differentiating primary from secondary types of polycythemia. They occasionally permit early detection of pulmonary abnormalities in patients in whom physical examination and x-ray studies cannot disclose certain disease in the lungs; it is possible that periodic use of a battery of pulmonary function tests to screen workers in industries with a dust hazard might well result in detection of early changes and so offer the opportunity to institute measures to prevent severe, permanent disability. Finally, in an analytic sense, pulmonary function studies indicate the specific function of the lung that has been impaired in pulmonary disease and give the physician a clearer concept of the disease process in each patient.

Before discussing individual function tests two general points deserve emphasis: (1) Clinicians are almost universally eager that physiologists agree upon a *single* pulmonary function test to serve all diagnostic and prognostic needs. In our opinion no single test can be so used to the exclusion of all others; some procedures are tests of ventilation, others of diffusion and still others of circulation. For some years to come a battery of tests must be used. If the results of these are correlated carefully with clinical impressions and surgical, radiologic and pathologic findings in a wide variety and large number of patients, eventually a simplification or improvement of the procedures now employed may emerge. (2) At present sufficient data have not been obtained upon large enough groups of *healthy* persons to determine with certainty what constitutes normal values for pulmonary function in healthy men and women of all age groups, and what values represent an irreducible minimum below which patients cannot live in comfort.

SPECIFIC TESTS OF PULMONARY FUNCTION

Arterial Blood Studies

Since the major function of the lung is to arterialize the venous blood (i.e., to add O_2 and remove excess CO_2), logically the first test of pulmonary function might be a study of *arterial* blood O_2 and CO_2. Analysis of peripheral *venous* blood serves no useful purpose because the O_2 and CO_2 in the antecubital vein blood, for example, depend not only upon the nature of the arterial blood entering the arm but also upon the local metabolism of the arm tissues and the rate of blood flow through them. Keys[33] has observed that O_2 saturation of such blood can be made to vary from 25 to 91 per cent at times when the *arterial* O_2 saturation is normal.

Studies upon arterial blood usually require that an actual sample of blood be drawn.[12] It is true that improved oximeters may eventually permit easy determination of absolute arterial O_2 saturation of blood as it is flowing through vessels in the body.[53] However, instruments of this type do not give information regarding the pH, CO_2 content and CO_2 pressure, and these data are often essential to the analysis of pulmonary function.

Arterial Oxygen Saturation and Pressure. Because of the nature of the oxygen dis-

sociation curve slight degrees of impairment in the oxygenating function of the lung result in a greater decrease in arterial O_2 pressure than in arterial O_2 saturation. The usefulness of measurements of arterial O_2 pressure has been discussed elsewhere in this symposium[46] and will not be considered here. Because measurements of arterial O_2 pressure are relatively new and technically difficult, the routine test for measurement of blood O_2 is the determination of arterial O_2 *saturation*. The errors of the method and steps required to avoid them are detailed elsewhere.[12]

Normal Values. Older methods, which failed to correct for technical errors, placed normal arterial O_2 saturation at 93 to 96 per cent. Recent data revise these figures upward to 97.4 per cent, SD ± 2.1. No information is available on variability from hour to hour or day to day in healthy adults. The arterial O_2 saturation is lower (96.1 per cent) in elderly men and women not suffering from cardiopulmonary disease.[32] It is also low in the newborn and appears to reach adult values at about two hours after birth.[17] When 100 per cent O_2 is breathed by healthy young adults, hemoglobin becomes fully saturated with O_2; in addition, the blood contains about 2.0 cc. O_2/100 cc. blood in excess of that required to saturate hemoglobin. This excess represents that in physical solution at the high O_2 tension to which blood is exposed.

Significance of Arterial O_2 Saturation Measurements. (1) A low value does not necessarily indicate the existence of pulmonary disease since anoxemia may occur in certain types of congenital heart disease with a right to left shunt, or in patients with inactive hemoglobin.* (2) There is no necessary relation between the level of arterial O_2 saturation in pulmonary disease and pulmonary disability. The terms pulmonary *insufficiency* and pulmonary *disability* are often used interchangeably. However, they are not synonymous. Pulmonary insufficiency refers to the inability of the lungs, because of pulmonary disease, to perform their function, i.e., to maintain arterial O_2 and CO_2 at proper levels.* Whenever the lungs cannot maintain arterial O_2 pressure and saturation at normal levels, pulmonary *insufficiency* exists *for the oxygenating function.* Whenever they cannot prevent arterial pCO_2 from rising above normal, pulmonary *insufficiency* exists *for the CO_2 eliminating function.* Pulmonary *disability* is present, however, only when the patient is unable to carry on a useful existence. Patients with arterial O_2 saturation in the 85 to 95 per cent range are not usually *disabled* on this account but from other causes, since their disability is rarely relieved by correction of anoxemia by O_2 therapy. The lower limit of arterial O_2 saturation compatible with moderately active existence depends upon many factors; certainly in patients with congenital heart disease or pulmonary hemangioma the saturation may be well below 80 per cent without producing disability. On the other hand, an asthmatic patient may, by increased effort, succeed in maintaining adequate alveolar gas exchange and normal arterial O_2 saturation, but only by performing an inordinate amount of work which results in dyspnea and pulmonary disability. Patients with pulmonary emphysema may be disabled despite the fact that arterial O_2 saturation is between 90 to 95 per cent; the arterial O_2 saturation in this disease depends upon the minute volume of breathing, the distribution of inspired gas to the alveoli and the amount of poorly ventilated lung tissue perfused by pulmonary capillary blood, whereas disability is more closely related to the work required in ventilation. (3) There is no necessary relationship between the *severity*

* If O_2 saturation is measured as the ratio of O_2 content (HbO_2 in arterial blood):O_2 capacity (HbO_2 when blood is exposed to the pO_2 in air in a tonometer), inactive forms of Hb may not be revealed; if O_2 saturation is measured spectrophotometrically as HbO_2:Total Hb pigment (active and inactive), inactive forms will be revealed.

* Arterialization of the venous blood may be incomplete if the inspired O_2 pressure is reduced or if respiration has been reduced because of central depression or neuromuscular disturbances. Such conditions are not classified as *pulmonary* insufficiency so long as the lungs themselves remain normal.

of pulmonary disease (so far as threat to life is concerned) and the arterial O_2 saturation. When diseased areas of the lungs receive no blood supply (cyst, carcinoma, some tuberculous lesions), arterial O_2 saturation remains normal as long as the remainder of the lung is adequate; even after pneumonectomy arterial O_2 saturation can be normal (at least in a resting patient) if the remaining lung is healthy. (4) Finally, one must not expect by measurement of arterial O_2 saturation to reveal the presence of pulmonary lesions which impair the oxygenation mechanism only slightly; a fall in arterial pO_2 from 100 (normal) to 80 mm. Hg (abnormal) causes the saturation to decrease by only 2 per cent which is within the error of analysis in some laboratories.

Further information can be obtained by measuring the arterial O_2 saturation during exercise and during inhalation of O_2. A fall in arterial O_2 saturation during exercise may be due either to a right to left-sided shunt or to serious pulmonary disease (impairment of diffusion or poor ventilation of well circulated areas). These may be differentiated by noting the effect produced by inhalation of O_2. Arterial blood can never contain the full calculated value for O_2 (that combined with Hb plus dissolved O_2) during inhalation of O_2 if a shunt is present whereas it approaches this closely in most other types of pulmonary disease. However, although inhalation of O_2 may reveal the existence of shunts it cannot differentiate between the anatomic shunts of congenital heart disease and pulmonary hemangiomas, and the complete functional shunts seen in parenchymal pulmonary disease such as atelectasis or bronchopneumonia.*

Arterial CO_2. As mentioned earlier, measurement of arterial CO_2 is often as valuable diagnostically as determination of arterial oxygen. Carbon dioxide content or pressure can be measured in whole blood or plasma. If one measures CO_2 content of whole blood, pH and arterial O_2 capacity, one can calculate the CO_2 pressure from nomograms.[48] Direct measurements of CO_2 pressure by bubble equilibration technics[12] are no more accurate and do not in themselves give a complete analysis of the acid-base changes. Normal values for blood CO_2 are given in Table 1.

TABLE 1
NORMAL VALUES FOR ARTERIAL O_2, CO_2 AND pH IN HEALTHY YOUNG ADULTS*

	Mean	S.D.
O_2 saturation, %	97.4	2.1
O_2 pressure, mm. Hg	97.1	2.5
CO_2 content, whole blood mM/L	22.2	0.9
vols. %	49.5	2.0
CO_2 content, plasma mM/L	26.9	0.9
vols. %	60.0	2.0
CO_2 pressure, mm. Hg	41.6	2.9
pH	7.39	0.03

* Compiled by SINGER, R. and HASTINGS, A. B. for "Handbook of Biological Data."

Significance of Blood CO_2 Values. (1) Elevation of CO_2 content of whole arterial blood or plasma does not necessarily indicate that there is primary pulmonary insufficiency for CO_2; it may represent primary chloride loss with compensatory retention of CO_2 as bicarbonate, i.e., alkalosis rather than respiratory acidosis. If, however, the blood CO_2 pressure and content are elevated and the pH is decreased it is certain that the lungs can no longer eliminate CO_2 adequately and respiratory acidosis has occurred. If the patient is hyperventilating at this time, this type of acidosis is certain to be due to pulmonary disease rather than to depression of the respiratory center. Since blood CO_2 content may be high or low in either alkalosis or acidosis, accurate measurement of pH should always be performed to differentiate these conditions. (2) Pulmonary insufficiency for CO_2 elimination is always accompanied by pulmonary insufficiency

* Douglas[19] has devised a somewhat similar method of differentiation which utilizes an oximeter and does not require blood gas analyses. He measures the mean alveolar pO_2 required to achieve 99.5 per cent saturation of hemoglobin. If a higher tension is required than in normal subjects, it is likely that there are venous additions to arterial blood (anatomic shunts, underventilation of circulated alveoli or impairment of diffusion).

for O_2 uptake (unless O_2 therapy is being administered, in which case the high O_2 pressure in inspired and alveolar gas causes the arterial blood to be well oxygenated). (3) The reverse is not necessarily true. CO_2 pressure may be normal or low at times when arterial O_2 saturation is definitely reduced as a result of pulmonary disease. The explanation is a simple one: Blood leaves poorly ventilated alveoli with a high CO_2 and low O_2 content; blood leaves hyperventilated alveoli with considerably lower than normal CO_2 content but with practically no increase above normal arterial O_2 content.* When blood from poorly ventilated and hyperventilated alveoli come together, the mixed arterial blood will be deficient in O_2 but normal or even low in CO_2. Blood CO_2 may thus be high, low or normal in patients with pulmonary disease. Normal or low CO_2 content and pressure do not mean that the patient is not seriously ill; it means that he still has alveoli capable of being hyperventilated but to achieve this he may be required to perform so much unaccustomed respiratory work that he is incapacitated. In this instance pulmonary disability has developed without pulmonary insufficiency for the function of CO_2 elimination.

Knowledge of the arterial O_2 saturation and CO_2 tension during breathing of air and of O_2 can thus be utilized to give information regarding the over-all ability of the lung to exchange O_2 and CO_2 and some of the mechanisms involved. For a more complete analysis, however, additional tests are required.

Frequency, Tidal Volume and Minute Volume of Breathing; Dead Space; Alveolar Ventilation

Tidal volume is the quantity of air that moves in or out of the nose and mouth with each inspiration or expiration. Minute volume is tidal volume times frequency of breathing per minute. Alveolar ventilation is the volume of inspired air that enters the alveolar sacs and participates in active gas exchange; it does not include that portion of the inspired gas which remains behind in the respiratory dead space of the nose, mouth, pharynx, trachea and bronchi.

Methods for measuring these volumes are described in detail elsewhere.[12] Normal values for minute volume are approximately 3.6 L./sq. M. body surface/minute for men and 3.2 for women.[1] Frequency of breathing and tidal volume vary considerably in normal subjects and it is difficult to give precise data. Tidal volume, frequency and minute volume are relatively easy to measure. Estimation of alveolar ventilation requires measurement of these values plus knowledge of the respiratory dead space. The latter is more difficult to determine but if the values obtained by Fowler (150 cc. for males and 110 cc. for females[22,23]) are applied reasonably accurate figures for alveolar ventilation can be calculated.

Significance of Values for Ventilation. Only by quantitative measurements can the physician know with certainty the volume of air moving in and out of the lungs. Some patients with pulmonary disease appear to be hyperventilating as far as external movements of the chest and abdomen are concerned but actually are breathing subnormal volumes of air; this is a common observation in patients with asthma, extensive bronchopneumonia or massive collapse of the lung.

It is true that careful examination by a fluoroscopist trained to look for disturbances in ventilation can reveal general hypoventilation, may localize geographically uneven distribution and determine if either is due to involvement of costal or diaphragmatic components. However, fluoroscopic examination cannot be made to yield quantitative data on small changes in gas volume. It is also true that the clinician may, by inspection, note whether the chest appears to be moving uniformly and adequately; by auscultation determine whether breath sounds indicate reasonably adequate

* Blood is 97 to 98 per cent saturated during quiet breathing; hyperventilation with air cannot raise the saturation more than 1 or 2 per cent above this value.

alveolar expansion; by the use of a tape, measure the expansion of the chest during quiet and maximal breathing; by percussion determine the excursion of the diaphragms in deep breathing. Again, although these may give useful impressions, they are not quantitative so far as volumes are concerned and are occasionally misleading. More often physicians attempt to judge the adequacy of ventilation by the color of the patient's skin without realizing that it is very difficult in this way to estimate the extent of arterial anoxemia[10] and impossible to determine the adequacy of the lungs in eliminating CO_2. Certainly one cannot gauge the adequacy of pulmonary ventilation by this method when O_2 is being administered to a patient with anoxemia. In this case the skin may become a healthy pink color (whether ventilation is adequate or not) because the high pressure of O_2 in the inspired and alveolar gas causes more O_2 to diffuse across the alveolar-capillary membrane into the blood; however, the inadequate ventilation prevents the proper elimination of CO_2 and respiratory acidosis develops.[11]

Quantitative measurements of minute volume should be made whenever there is doubt about the adequacy of ventilation. If there is insufficient movement of air, measures should be instituted to increase the minute volume.

The amount of air moving in and out of the nose and mouth is not so important as the quantity that aerates the pulmonary alveoli. A simple example illustrates this point. Assume that each of two patients has a respiratory dead space of 150 cc. and each breathes 8,000 cc./min. but that the first has a tidal volume of 1,000 cc. and a frequency of 8/min., while the second has a tidal volume of 200 cc. and a frequency of 40/min. The first then has an alveolar ventilation of 6,800 cc./min. ((1,000 cc.–150 cc. dead space) × 8) while the second has an alveolar ventilation of only 2,000 cc./min. ((200 cc.–150 cc. dead space) × 40).

Despite the value of knowing minute volume and alveolar ventilation, it must be emphasized that pulmonary gas exchange may be inadequate even though the volume of alveolar ventilation is normal, if air is distributed largely to diseased alveoli which have poor pulmonary blood flow or if there is impairment of diffusion across the alveolar capillary membrane owing to thickening of the alveolar component, the capillary component or to actual separation of these membranes by interstitial edema. These conditions again illustrate the hopelessness of attempting to analyze pulmonary dysfunction by a single test, no matter how carefully this be done.

Ventilation Equivalent; Ratio of O_2 Removal

The *ventilation equivalent for O_2* is the number of L. of air breathed per 100 cc. O_2 consumption. The *ratio of O_2 removal** is the reciprocal of this × 100 i.e., cc. O_2 uptake per L. air breathed. If the minute volume of breathing is 5 L./min. and the O_2 consumption is 250 cc., the ventilation equivalent is $\frac{5}{2.5}$ or 2, and the ratio of O_2 removal is $\frac{250}{5}$ or 50. Normal values are approximately 2.2 to 2.5 and 40 to 45, respectively.

Significance of These Ratios. They are believed to be helpful in two ways: (1) To determine some of the factors involved in producing hyperventilation. In hyperpneas associated with primary increase in tissue metabolism (exercise, fever, hyperthyroidism) rise in O_2 consumption parallels increase in ventilation and the ratio of O_2 removal remains more or less normal. In pulmonary disease, tissue metabolism and O_2 consumption remain approximately normal but ventilation may be augmented by a decrease in arterial O_2 pressure or by a variety of pulmonary reflexes; in such cases the ventilation equivalent increases or the ratio of O_2 removal decreases. In practice the test is rarely needed for this

* This is commonly called "*rate* of O_2 removal." "Ratio" is preferable because only the ratio of two volumes and not volume per unit time is involved.

purpose. Furthermore, when the test does indicate that ventilation is abnormally high in relation to metabolism it gives no clue as to the cause, whether pulmonary or otherwise. (2) To provide an estimate of the adequacy of pulmonary blood flow. The principle on which this estimate is based is as follows: The tissues by utilizing O_2 reduce the O_2 content in venous as compared with arterial blood. The quantity of O_2 withdrawn from the systemic capillaries is restored in the pulmonary capillaries if sufficient O_2 is supplied to the alveoli by the process of ventilation and if this O_2 passes rapidly through the alveolar capillary membrane by the process of diffusion. The O_2 taken up in the lungs must also depend upon the volume of blood flow through the pulmonary capillaries. If tissue usage of O_2 be increased and held reasonably constant by a steady rate of exercise, a high ratio of O_2 removal would imply a greater capacity for increase in pulmonary blood flow than in pulmonary ventilation and diffusion, and a lower ratio of O_2 removal might imply a greater capacity for increase in pulmonary ventilation and diffusion than in pulmonary circulation. Unfortunately, many factors determine the magnitude of these ratios and such a simple interpretation is usually unjustified, particularly in patients with pulmonary disease. In the opinion of Baldwin, Cournand and Richards[1] the use of these ratios to differentiate circulatory from pulmonary insufficiency is completely unwarranted without consideration of information obtained from other tests. These ratios do have a place, however, in the analysis of individual lung function.

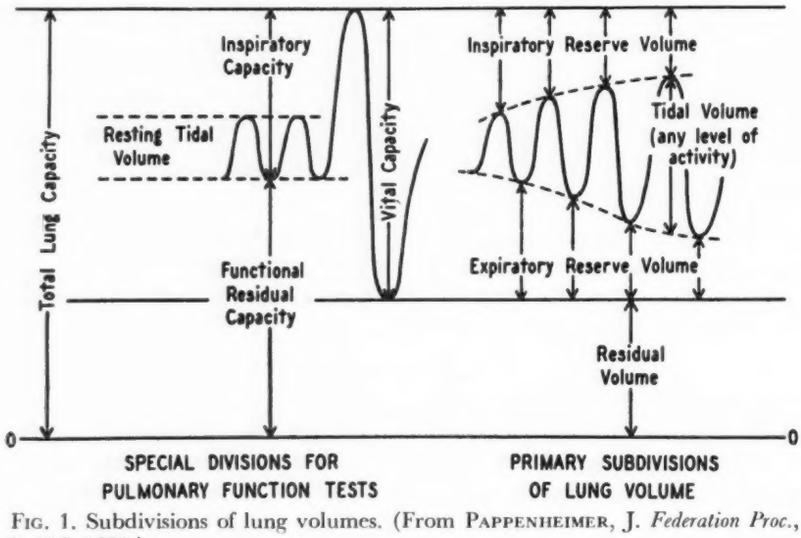


FIG. 1. Subdivisions of lung volumes. (From PAPPENHEIMER, J. *Federation Proc.*, 9: 602, 1950.)

Lung Volumes

Christie, in 1932, stated "In perhaps no realm of physiology is there a more confusing medley of terms than in that which deals with the lung volume and its various subdivisions."[8] To remedy this confusion a committee of respiratory physiologists[42] has recently agreed upon the following terminology and definitions (Fig. 1):

Vital capacity is the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration.

Inspiratory capacity (complemental or complementary air) is the maximal volume of gas that can be inspired from the resting end-expiratory level.

Inspiratory reserve volume (complemental or complementary air, complemental air minus tidal air, inspiratory capacity minus tidal volume) is the maximal amount of gas that can be inspired from the end-inspiratory position.

Expiratory reserve volume (reserve or supplemental air) is the maximal volume of gas that can be expired from the resting end-expiratory position. In function studies the *resting* end-expiratory position is always used.

Functional residual capacity (functional residual air, sub-tidal volume, equilibrium capacity, normal capacity, mid-capacity) is the volume of gas remaining in the lungs in the resting, end-expiratory position.

Residual volume (residual capacity, residual air) is the volume of gas remaining in the lungs at the end of a maximal expiration.

Total lung capacity is the sum of vital capacity and residual volume; in other words, it is the maximal amount of gas that can be contained in the lung when it is fully expanded.

Vital Capacity and its Subdivisions

Details of the procedure for the measurement of vital capacity are given elsewhere.[12]

Normal Values. The measured vital capacity in any patient may be evaluated by comparison either with normal data for each age group (with due consideration for any striking variation in height and weight of the individual) or with data derived from formulas. Formulas commonly used for calculation of vital capacity are:

Based on	Males	Females	Reference
Surface area	2.5 L./M²	2.0 L./M²	(52)
Height	25 ml./cm.	20 ml./cm.	(52)
Height and age	27.63— (0.112 x age) x height in cm.	21.78— (0.101 x age) x height in cm.	(1)

None of the above formulas applies to children; separate tables are required. Vital capacity is approximately 300 cc. less when measured in the supine position as compared with the standing position; this is due largely to differences in pulmonary blood volume.[40]

A vital capacity measurement in any single healthy individual may deviate from the group mean or calculated figure by as much as 20 per cent. Thus there is considerable difficulty in evaluating a single borderline (low) vital capacity measurement. However, vital capacity measurements are useful in measuring changes in the same individual over a period of time. Recent studies indicate that variations in excess of 220 cc. have real significance.[39,44]

Significance of Measurements of Vital Capacity. Physically the vital capacity test measures a volume of gas, the maximum that can be expelled from the lungs by forceful effort after a maximal inspiration. This volume of gas may be reduced by a number of factors. In some instances decrease in vital capacity is the result of *disease or alterations in the pulmonary parenchyma;* examples of parenchymal involvement include bronchogenic tumor, edema, fibrosis, infection, atelectasis, localized obstruction of the airway, pleural adhesions or surgical excision of lung tissue. However, a much larger list of *non-pulmonary factors* may reduce the vital capacity. These include: (1) unwillingness on the part of the patient to cooperate, (2) inability to comprehend or to cooperate fully, (3) depression of the respiratory centers in the medulla, (4) disease of the motor nerve tracts, anterior horn cells, peripheral motor nerves, neuromuscular junction or of the skeletal muscles themselves, (5) limitation to chest expansion caused by certain bodily positions, tight strapping, scleroderma, bony deformities or thoracic pain (pleurisy, fracture of a rib, or thoracic or upper abdominal incisions), (6) limitation to the descent of the diaphragm due to pregnancy, ascites, abdominal tumor, pneumoperitoneum or paralysis of the phrenic nerve, (7) encroachment upon relatively normal alveoli by pleural effusion, artificial pneumothorax, diaphragmatic hernia, elevation of the diaphragm, marked enlargement of the heart, large pericardial effusion or congestion of the pulmonary capillary bed.

Reduction in vital capacity is, then, not pathognomonic of any specific pulmonary disease and indeed does not necessarily signify pulmonary disease at all. On the

other hand, it is possible that a patient may have pulmonary disability even though his vital capacity is in the normal range; this is so commonly observed in emphysema that the simple volume measurement of vital capacity is notoriously unreliable in this condition. Therefore one cannot rely upon vital capacity as an isolated test of pulmonary function.

Measurements of vital capacity are of more value when repeated observations are made upon the same individual to follow spontaneous changes in cardiopulmonary disease or to determine the effect of treatment. They are also of diagnostic use when considered in relation to time or to the values for maximal breathing capacity.[28,37]

Measurements of vital capacity alone are helpful in determining the degree of bronchial obstruction only when the value rises significantly after the administration of potent bronchodilator drugs.

Significance of Changes in Inspiratory Capacity and Expiratory Reserve Volume. As an approximate guide, the inspiratory capacity normally is 75 to 80 per cent of the vital capacity and the expiratory reserve volume 20 to 25 per cent. However, the expiratory reserve volume is subject to considerable variability even in the same individual; Christie noted an average deviation of ± 78 cc. and a maximal deviation of 316 cc. from mean values in normal subjects. Normal values for large groups vary from 980 to 1,980 cc.[7,12] Position is an important factor. Osher found that the expiratory reserve volume diminished 860 cc. upon change from the erect to the supine position.[41]

Possibly because of difficulty in interpreting changes in these two fractions of vital capacity, very few investigators have reported data upon these volumes. In general, however, considerable attention is given to values for residual volume.

Residual Volume (RV) and Functional Residual Capacity (FRC)

The residual volume, the volume of gas that remains in the lung at the end of a forced expiration, is the only one of the lung volumes that cannot be obtained by direct tracings on a spirometer and must be measured by indirect means. The method used most widely in this country is the open circuit method of Darling and associates[18] in which the subject breathes 100 per cent O_2 for a period of seven minutes and the volume of N_2 washed out of the lungs during this time is measured. The residual volume is not measured directly but the functional residual capacity (residual volume and expiratory reserve volume) is measured and the expiratory reserve, determined separately, is then subtracted from it to obtain the residual volume. The technic of this procedure, its errors and alternate methods have been described in full elsewhere.[12]

Normal values for residual volumes and RV/TC ratios are given in Table II. Rahn and associates found that day to day variations in residual volume were 5.5 per cent (average standard deviation) as compared to 7.9 per cent variation in expiratory reserve and 1.9 per cent in vital capacity.[44]

Signficance of Changes in RV/TC Ratio. An increase in this ratio does not necessarily signify that the absolute value for residual volume is also greater than normal. The fraction $\frac{\text{residual volume}}{\text{total lung capacity}} \times 100$ can increase if either the absolute residual volume is increased or the total lung volume is decreased, residual volume remaining approximately normal.

Significance of an Absolute Increase in Residual Volume. This is usually assumed to represent emphysematous changes in the lungs. Actually this represents *hyperinflation* rather than true emphysema. Hyperinflation may occur as a result of (1) structural changes such as diminution in the elastic fibers of the lung, tearing of alveolar septa and reduction in the pulmonary vascular capillary bed (true emphysema), (2) obstruction to the airway (asthma, etc.), (3) compensatory overinflation of the lung following surgical removal of lung tissue, (4) deformity of the thorax,[34] (5) decrease in elasticity of the lung such as appears to be a natural accompaniment of old age and (6) a variety of

pulmonary disorders including congestive heart failure and certain types of pulmonary fibrosis.[49]

It is not generally recognized that hyperinflation of the lung does not in itself produce pulmonary disability. A number of elderly individuals who have a marked increase in functional residual capacity and residual volume (the latter amounting to 40 or 50 per cent of total and, in this case, normal lung capacity) have been found to have no pulmonary incapacity.[32] An increase in functional residual capacity uncomplicated by obstruction will have little effect upon the diffusion of gases between blood and alveoli because intra-alveolar mixing and diffusion take place almost instantly even though the individual alveoli be hyperinflated. It will, of course, reduce the rate of turnover of alveolar gas but this will become apparent only when gases other than air are inhaled; for example, other things being equal, the rate of N_2 washout during inhalation of O_2 will be slowed, and the rate of increase in alveolar concentration of CO_2 or ether will be slowed when CO_2 or ether is added to inspired gas. An increase in functional residual capacity means that the thorax is always larger than normal; because of this abnormal position, some muscular inefficiency and mechanical disadvantage may result.

Residual volume and functional residual capacity are usually increased together. In some instances residual volume may be increased without increase in functional residual capacity (if expiratory reserve volume decreases sufficiently). An increase in residual volume occurring without increase in total lung volume must mean that the vital capacity is reduced. However, breathing reserve is not necessarily reduced on this account since the full vital capacity is rarely used to achieve additional or maximal ventilation.

Residual volume is decreased in diffuse fibrosis of many types and in many diseases in which alveoli are occluded in many portions of the lung.

Total Lung Capacity (T.C., Total Volume, Total Lung Volume)

This is the sum of the inspiratory capacity and functional residual capacity (or of the vital capacity and residual volume). Normal figures are presented in Table II. It may be computed from calculated normal vital capacity by multiplying vital capacity by 0.80 for the age group fifteen to thirty-four years, by 0.766 for thirty-five to forty-nine years, and by 0.692 in the group over fifty. Total capacity may vary from the estimated normal by ± 15 to 20 per cent in healthy subjects.

TABLE II
NORMAL LUNG VOLUMES*
(LITERS; 37°C. SATURATED WITH WATER VAPOR; SUBJECTS RECUMBENT)

	Young Males		Older Males		Young Females	
	Mean	S. D.	Mean	S. D.	Mean	S. D.
Age, years	22.9	3.3	48.2	6.4	23.1	3.4
Height, cm	176.2	5.1	170.5	7.2	163.4	4.2
Weight, kg	72.5	11.2	70.8	12.1	57.2	9.4
Inspiratory capacity	3.79	0.52	3.37	0.57	2.42	0.36
Expiratory reserve volume	0.98	0.26	0.69	0.31	0.73	0.19
Vital capacity	4.78	0.59	4.07	0.62	3.14	0.41
Residual volume	1.19	0.35	1.30	0.41	1.10	0.30
Total lung capacity	5.97	0.81	5.37	0.84	4.24	0.57
Functional residual capacity	2.18	0.50	2.00	0.50	1.82	0.39
RV/TC × 100	19.8	4.4	24.5	5.5	25.9	5.0

* From KALTREIDER, N. L., FRAY, W. W. and HYDE, H. V. Z. *Am. Rev. Tuberc.*, 37: 662–689, 1938.

Radiologists have attempted to measure residual lung volume and total lung volume from planimetric tracings of films of the chest taken in several planes. Good approximations may be obtained in normal individuals who have no pulmonary disease, since radiologic chest volume (minus cardiac volume) is closely related to the pulmonary gas volume.[29] Differences between chest volume and gas volume (determined by measurement of functional residual capacity) might give a closer measure of "lost" gas volume in any individual than comparison of measured and predicted total lung volumes. However, in patients with parenchymal lung disease or vascular congestion, correlation is poor.

The total lung capacity is decreased in patients who have diffuse pulmonary fibrosis, large mass lesions of the lungs, or have pulmonary tissue compressed (by congestion, pneumothorax, hydrothorax) in such a manner as to prohibit compensatory over-distention of other parts of the lungs. Total lung capacity may be normal in the presence of large cysts in open communication with the air; it may be low if these are closed.[4] It may remain normal in the presence of fibrosis if the latter is of a type which leads to hyperinflation.[49] Total lung capacity may be normal or slightly increased in emphysema. It is increased by pressure breathing.

TABLE III
MAXIMAL BREATHING CAPACITY (L./MIN.) IN NORMAL MALES AND FEMALES IN DIFFERENT AGE GROUPS[1]

Age Group	No. of Subjects	Range	Mean	S. D.
Males:				
16–34*	17	82–169	126†	±28.6
35–49	15	86–144.5	109.4	±15.9
50–69	18	58–139	90.6	±16.8
Females:				
16–34	15	63.6–117.5	93.7‡	±12.6
35–49	10	47.0–114	89.3	±17.9
50–69	13	49.0–101.5	73.5	±16.8

* Gray and associates find no decrease with age between 18 and 35 years.[31]

† Other investigators report this figure as 147, 154, 166 and 169 L./min. (During breathing of 80 per cent He, 20% O_2, values of 176–210 have been reported).

‡ Gray reports this as 115.8 L./min. (S.D. ± 21).[31]

Normal total lung capacity does not imply that total lung diffusing surface is normal in quantity or in its properties; coalescence of several alveoli into one (by tearing of septa) reduces surface but not volume.

Maximal Breathing Capacity (MBC)

Maximal breathing capacity (voluntary ventilation capacity, maximal minute ventilation or maximal voluntary ventilation) is defined as the maximal volume of gas that can be breathed per minute. It can be attained only by voluntary effort; inhalation of 10 per cent CO_2 or severe muscular exertion (bicycle, treadmill) rarely produces the maximal ventilation of which an individual is capable.[20] The patient is instructed to breathe as deeply and as rapidly as he can through a low resistance system for 15 seconds. The patient should be permitted to choose his own frequency and tidal volume; the frequency is usually between 40 and 70 /min. and the tidal volume about 50 per cent of vital capacity. Maximal figures are rarely attained by insisting upon repeated performance of the entire vital capacity because the extremes of inspiration and expiration are performed with undue expenditure of time and energy.

Formulas in common use for the calculation or prediction of maximal breathing capacity are as follows:

Sex	Formula	Reference
Females. .	[71.3 − (0.474 x age] x sq.m.s.a.	Baldwin (1)
Males. . . .	[86.5 − (0.522 x age] x sq.m.s.a.	Baldwin (1)
Males. . . .	228 − (1.82 x age) ± 17.6%	Wright (12)

Normal Figures for Maximal Breathing Capacity. Normal figures obtained in different laboratories vary by as much as 32 per cent according to the type of apparatus used and the resistance it offers to breathing. Until similar apparatus and procedure are employed universally it seems inevitable that each laboratory must calibrate its own apparatus and secure its own normal standard values. Unfortunately, it is not sufficient to secure normal data only for young healthy adult males since values in healthy females and elderly males and females are considerably lower. Table III illustrates the change that occurs in MBC in older age groups; no data are available for children. Because of the large standard deviation a healthy person may deviate by 25 to 35 per cent of mean group values; consequently, reduction in maximal breathing capacity must be large to be significant.

Most of the figures for normal maximal breathing capacity have been obtained

upon healthy medical students. It is not strictly justified to compare values obtained upon patients with these because the test requires the maximal respiratory muscular effort of which the patient is capable, and a desire to cooperate even to the point of exhaustion. Not every patient is motivated to this extent and some, especially compensation cases, may even be maligners; Cournand has advised that CO_2 be added to the inspired air to detect these.

The maximal breathing test does not require considerable training; maximal values are usually obtained after one practice effort has been made.[31] There are few data concerning the variability in maximal breathing capacity in healthy individuals day by day over a period of months.

Significance of Maximal Breathing Capacity Values. The maximal breathing capacity test is obviously more than a simple measurement of lung volume. It does not correlate well with vital capacity even in normal individuals.[1,15,37] The ability of a patient to breathe at sustained high velocity depends upon factors in addition to vital capacity; these probably include muscular force, patency of airways, pulmonary elasticity and distensibility. Maximal breathing capacity is, of course, often reduced when vital capacity is small but it may be relatively unaffected in some instances in which vital capacity is decreased and markedly reduced in other cases in which vital capacity is normal.

In general, maximal breathing capacity is reduced out of proportion to decrease in vital capacity in patients with obstruction of the airways or with diminution in elasticity of the lung tissue. The mechanism in obstruction is obvious; the other, less so. Expiration is aided in normal individuals by the elastic recoil of the lungs; whenever elasticity is decreased, the act of expiration requires greater muscular effort, is apt to be prolonged, and the maximal breathing capacity decreases. Patients with emphysema generally have low maximal breathing capacity because several factors may be present: obstruction, diminished elasticity and mechanical difficulty because of the inspiratory position of the chest. If maximal breathing capacity is low and rises more than 10 per cent after administration of a potent bronchodilator agent, this indicates that a reversible type of bronchial obstruction was one component involved.

Maximal breathing capacity is fairly well maintained, even in association with marked reduction in vital capacity in some patients with pulmonary fibrosis.[2,57] The reason for this appears to be as follows: Healthy subjects rarely employ the full inspiratory excursion in the performance of the maximal breathing capacity test. Consequently a decrease in the inspiratory capacity component of vital capacity does not reduce the maximal breathing capacity significantly if there is no associated obstruction of the airways or loss of elasticity. The normal individual may breathe 50 per cent of a vital capacity of 4,000 cc. or 2,000 cc. with each breath in the performance of the maximal breathing capacity test. Patients with limitation of inspiration may use 66 per cent of a vital capacity of 3,000 cc., again 2,000 cc., during the maximal breathing capacity test, and do so without entering the extreme zones of decreased mechanical efficiency. This has been observed in healthy individuals subjected to tight strapping of the chest.

Realizing that more information can be obtained from a comparison of the vital capacity and maximal breathing capacity in the same individual than from consideration of only one of these factors, investigators have compared the two tests by means of several ratios.[28,37] Gaensler[27,28] relates the two as follows:

$$\frac{\text{per cent of predicted maximal breathing capacity}}{\text{per cent of predicted vital capacity}} = \text{air velocity index}$$

Patients with obstruction of the airway had an index of considerably less than one whereas those with loss of functioning parenchymal lung tissue (including that following

thoracoplasty and pneumothorax) had an index above one. This index may be misinterpreted if it is used without the absolute figures from which it is derived, since an index of one may result from proportionate *reduction* in *both* maximal breathing capacity and vital capacity.

Although the maximal breathing capacity gives some information regarding the mechanics of breathing in many types of pulmonary disease, in general it depends upon so many factors that a low value merely indicates that an abnormality exists and is not pathognomonic of any single disease. Furthermore, it is a needlessly exhausting test and almost certainly will be replaced within the next few years by simpler tests utilizing a single breath or by measurements of work of breathing and resistance to air flow; tests of these functions are considered in another article in this series.[21]

Spirograms

Spirographic tracings of normal breathing, vital capacity and maximal breathing capacity made upon a rapidly moving kymograph provide not only a permanent record for comparison with later tracings but also permit analysis of many characteristics of the breathing pattern. Some of these are: (1) *Times for normal inspiration and expiration.* Normally, expiration requires about 1.2 times as long as inspiration. In expiratory obstruction and in emphysema (in which the elastic recoil, which normally aids expiration, is diminished) expiratory time is prolonged. (2) *Rates of normal and maximal inspiration and expiration.* Normally, air flow is rapid and results in steep inspiratory and expiratory slopes, with the exception of the terminal portions. In emphysema although the volume of vital capacity may be normal the rate of air flow is slowed throughout but particularly during the latter half of expiration; as much as twenty seconds may be required to expel the vital capacity.[30] Air flow is also slower than normal at end inspiration. In asthma flow is retarded especially in expiration. In congestive heart failure flow is slower for the last 200 cc. of both inspiration and expiration.[15] (3) *Time for return to resting expiratory level.*[9] If a normal individual inspires maximally and then permits his chest to return passively to the resting expiratory level, all of the inspired air is expelled before the next inspiration occurs. In patients with obstruction that is predominantly expiratory this maneuver is followed by a slow step-like return to the normal baseline during which several breaths may occur before the resting expiratory level is reached. This phenomenon may be noted to an even greater degree in emphysema, partly because of associated obstruction and partly because after rapid overdistention of the lung the lung returns more slowly to its original volume.[9] This may become more evident during performance of the maximal breathing capacity test during which the chest moves progressively into the inspiratory position. This abnormally slow return to the resting expiratory level may also occur after a rapid maximal expiration. (4) *One- and two-stage vital capacity.* The "two-stage vital capacity" refers to the procedure in which the inspiratory capacity and expiratory reserve are determined separately and then added. In asthma and emphysema the "two-stage" value may exceed the "one-stage" by as much as a liter. If the "two-stage" value is smaller than the "one-stage," it is likely that the subject is not cooperating fully.[1]

Breathing Reserve

The breathing reserve of an individual is the difference between the maximal breathing capacity and the minute volume of breathing. The breathing reserve ratio or index is $\frac{\text{breathing reserve}}{\text{M B C}} \times 100$. These values can be calculated for resting or exercising patients. Thus if the maximal breathing capacity of an individual is 160 L. /min. and the minute volume is 6 L. /min., the breathing reserve is 154 L. and the ratio is 96.3 per cent. If the same individual is then made to exercise and his minute vol-

ume of breathing rises to 100 L./min., his breathing reserve becomes only 60 L /min. and the ratio 37.5 per cent.

Normal values for breathing reserve ratio of resting subjects are 95.9 per cent (S.D. ± 0.72)[38] and 91 to 95 per cent.[1]

Breathing reserve may be reduced either because of a reduction in maximal breathing capacity or because of an increase in the minute volume of breathing. A large reduction in resting breathing reserve, clinically, is almost always due to a decrease in the maximal breathing capacity since the minute volume of resting patients with pulmonary disease rarely exceeds 20 L./min.

There have been a number of attempts to correlate the breathing reserve or breathing reserve ratio with the subjective complaint of dyspnea. In an earlier study Cournand and associates stated that dyspnea usually occurred in their patients when the breathing reserve ratio fell to 60 to 70 per cent.[15a] However, Baldwin, Cournand and Richards,[3] in 1949, found this symptom to occur in different groups when the breathing reserve was 56, 41, 34 and 39 per cent of the maximal breathing capacity. Normal individuals exercising on a bicycle likewise experience dyspnea at entirely different levels of minute volume of breathing;[20] some had no dyspnea despite minute volumes as high as 114 L./min. while others had severe dyspnea at levels of only 50 L./min. The minute volume of breathing at which a patient experiences dyspnea is a useful clinical observation. To this reviewer, however, the additional calculation of breathing reserve adds little to the information obtained from the maximal breathing capacity test.

Exercise Tests

Among the commonly employed exercise tests are walking on a treadmill (ideal if the equipment is available), pedalling a stationary bicycle, walking along a level hallway and repeated stepping up on a platform and down again. Baldwin and associates[1] require their patients to step up and down on a platform 20 cm. high thirty times in one minute. This exercise is simple to perform but has certain disadvantages compared to the first three: (1) the effort expended during this performance varies according to the subject's degree of cooperation, (2) the duration of exercise is far too short to permit the development of a steady state, (3) the duration of the recovery period is too short for the measurement of the oxygen debt and (4) the exercise is so mild that it taxes only the obviously handicapped subject and cannot be expected to demonstrate incipient cardiopulmonary disability.[1] Pulse, blood pressure minute volume of breathing, frequency of respirations, O_2 consumption, CO_2 elimination, arterial O_2 saturation and subjective reactions (dyspnea, palpitation, fatigue) may all be measured or recorded during and after the exercise. Exercise tests are usually employed in pulmonary disease to correlate effort and dyspnea and to determine the effect of exercise upon arterial O_2 saturation.

Exercise and Dyspnea. Patients with many types of pulmonary disease often first become aware of dyspnea during exercise. Rather than depend solely upon the patient's estimate of his exercise tolerance it is possible to determine by quantitative tests the precise rate of walking, pedalling or stepping at which the patient becomes dyspneic. Warring[51] has used a "walking ventilation test" in which the operator and the patient walk slowly and uniformly over a measured level course covering 180 feet at a rate of about 2 miles per hour. During this walk the subject's expired gas is collected in a Douglas bag during the second, third and fourth minutes. The degree of dyspnea and its onset in relation to time and to minute volume of breathing are recorded. A ratio, $\frac{\text{walking ventilation}}{\text{maximal breathing capacity,}}$ is calculated. Warring has found that with ratios of 0.3 or less patients are usually not dyspneic when walking on the level; at 0.35, slight dyspnea occurs; at 0.45, moderate dyspnea; and at 0.5, severe dyspnea. However, since Warring found that prac-

tically every patient had a remarkably constant minute volume from day to day as long as the speed and distance remain constant (irrespective of the progression or regression of disease, or degree of collapse therapy), it appears to be unnecessary to measure the numerator in this ratio. Indeed, it may be questioned whether the ratio has great value, for practically the same information can be obtained by requiring the patient to walk over the same course at the same rate on different occasions and merely noting whether dyspnea develops. If dyspnea develops earlier (progression of disease, etc.) one could, from Warring's data, assume that maximal breathing capacity has decreased.

Exercise and Arterial Oxygen Saturation. Arterial O_2 saturation does not decrease during severe exercise in normal subjects. A decrease in saturation upon exertion does occur in certain pathologic states: (1) In patients with right to left shunts, intracardiac or intrapulmonic, a decrease is due to passage of a greater fraction of venous blood through the shunt when vascular pressures rise during exercise or to the fact that venous blood returning from exercising muscles has a lower O_2 content than that from resting muscles. (2) In patients with functional shunts (well circulated areas of the lungs are poorly ventilated), arterial O_2 saturation can decrease during exercise because the venous blood, containing less O_2 than normally, flows more rapidly through poorly ventilated alveoli. (3) In patients with marked reduction in diffusing area or diffusing capacity of the lung for O_2 the ability of the lung to transfer O_2 is reduced and, at a certain point, they will no longer be able to saturate increased volumes of poorly oxygenated venous blood per unit time. (4) In patients with marked restriction of breathing a relative hypoventilation occurs during exercise.

Decrease in saturation during exercise is usually interpreted as a sign of advanced pulmonary disease[2–4] in the absence of anatomic shunts. In cases of anatomic shunts inhalation of 100 per cent O_2 should not prevent a fall in saturation during exercise; in the other types it usually will.

Distribution of Inspired Air (Intrapulmonary Gas Mixing)

Evaluation of pulmonary function also involves measurement and analysis of the evenness with which the inspired air is distributed among the millions of alveoli in the lung. If alveolar ventilation were perfectly uniform each alveolus would, during inspiration, receive at the same time gas of the same chemical composition and of the same volume (in relation to its previous pre-inspiratory volume) and this gas would mix almost instantaneously with the functional residual gas in each alveolus. Uneven distribution can obviously lead to underventilation of some alveoli and overventilation of others and, depending upon the distribution of the pulmonary capillary blood flow, can lead to pulmonary insufficiency for oxygenation and eventually for CO_2 removal.

Methods designed to measure the evenness of distribution have been reviewed recently by Fowler.[24] Unfortunately, methods which are most precise and least objectionable from a theoretic point of view[5,6,25,26,27] are not ideal for routine clinical use because they are complex, expensive or time consuming. A relatively simple test, devised by Cournand Baldwin, Darling and Richards,[16] may be used as a measure of grossly abnormal distribution. In this test the patient breathes O_2 for seven minutes and at the end of this period delivers an alveolar gas sample which is analyzed for nitrogen concentration. If the inspired O_2 is distributed uniformly throughout his alveoli, it will wash alveolar nitrogen out of all parts of the lungs so uniformly that, at the end of seven minutes, very little nitrogen will remain in any. On the other hand, if the distribution of the inspired O_2 is non-uniform, hypoventilated areas tend to retain much of their nitrogen until it is forced out of them by the final maximal expiration at the end of seven minutes; the nitrogen concentration in such an alveolar sample will

be abnormally high. Cournand and associates have placed the upper limit of normal at 2.5 per cent nitrogen.[16]

This test is not solely a measurement of the distribution of inspired air; it is influenced also by the volume of breathing and the volume of alveolar gas. Table IV shows that a normal lung with a functional residual capacity of 2,500 cc., receiving a normal effective tidal volume of 500 cc. fifteen times per minute, will contain only 4.7 per cent nitrogen after oxygen is inhaled for a period of one minute. If this same lung be hypoventilated, it will contain 19.5 per cent nitrogen; whereas if it be hyperventilated, it will contain only 1.4% nitrogen. Thus if the frequency of breathing remains constant the final concentration varies with the tidal volume, even if the distribution of the inspired oxygen is perfect. On the other hand, if the functional residual capacity is abnormally high, let us say 4,500 cc., the nitrogen concentration in the alveolar gas will be high following inhalation of O_2 for one minute, even if the tidal volume is normal. Since the final alveolar concentration of nitrogen, measured by the Cournand emptying rate test at the end of seven minutes, is influenced by the lung volume, the effective tidal volume and the frequency of breathing as well as by the distribution factor, it is obvious that the test can be falsely positive, as far as the distribution is concerned, if the functional residual capacity is large in relation to the ventilation, or can be falsely negative if the functional residual capacity is small relative to the ventilation. These factors were well appreciated by Cournand and his group but they found the test to be clinically useful in the diagnosis of severe emphysema because in this condition the functional residual capacity is usually increased, the tidal volume may be decreased and distribution is decidedly abnormal. However, emphysematous patients who are still capable of hyperventilating may reduce the nitrogen concentration by the end of the seven-minute period so that the test gives a normal figure. Comroe and Fowler[14] found that the Cournand test was positive in only 32 per cent of a group of patients, 78 per cent of whom had abnormal distribution when measured by a more sensitive method utilizing rapid gas analyzers, such as the nitrogen meter. Such tests are objective, more sensitive, relatively simple to use once the equipment is constructed but the initial expense is beyond the means of most clinics.[25]

TABLE IV
PER CENT NITROGEN REMAINING IN ALVEOLAR AIR AFTER BREATHING OXYGEN FOR ONE MINUTE (FIFTEEN BREATHS)

When the Effective Tidal Volume Is (cc.)	When Functional Residual Capacity Is	
	2,500 cc.	4,500 cc.
750	1.4	8.8
500	4.7	17.0
250	19.5	38.0

The measurement of the distribution factor does not in itself afford a complete evaluation of pulmonary ventilation since it does not take into account the work of breathing and the evenness of distribution of pulmonary capillary blood flow to the ventilated alveoli (ventilation perfusion ratios).

Significance of Tests of Distribution of Inspired Gas. A widely held opinion is that unevenness of distribution is synonymous with emphysema. However, there is ample reason to expect the occurrence of uneven distribution in numerous other pulmonary diseases.[13] The manner in which inspired air is distributed depends upon many factors which influence the timing and extent of alveolar ventilation. Some of these factors are as follows: (1) Decreased distensibility of certain areas of the lungs, (2) regional obstruction of air passages and (3) loss of elasticity in certain areas of the lungs. There may, of course, be combinations of changes in distensibility, elasticity and patency of the airways in the same or different regions of the lung. For this reason it is important to

emphasize that an abnormality in the gas distribution factor revealed by a sensitive test is not necessarily an indication of the existence of emphysema. Comroe and Fowler have found abnormal distribution in a large percentage of patients with asthma, emphysema, bronchiectasis, sarcoid, congestive heart failure, pulmonary carcinoma, postpneumonectomy cases and a group of miscellaneous diseases of the lung.[14] The great majority of patients with emphysema have uneven distribution and to a greater extent than do other groups; it is for this reason that relatively insensitive tests are able to differentiate emphysematous patients.

Diffusing Capacity of the Lung

Impairment of diffusion and methods for its detection have been discussed by Riley in another article in this series.[46]

Pulmonary Circulation: Alveolar Ventilation-Perfusion Ratios

Uniformity of distribution of inspired gas has already been discussed; uniformity of distribution of pulmonary capillary blood flow is equally important. Continued ventilation of alveoli with poor or no circulation is equivalent to enlargement of effective respiratory dead space and results in hyperventilation of the whole lung, extra work and eventually to dyspnea. Persistence of circulation through poorly aerated alveoli creates a functional shunt and anoxemia. A new approach to the analysis of distribution of pulmonary capillary blood has been presented by Rahn,[43] and Riley and Cournand.[45]

Measurements of pulmonary vascular pressures are outside the scope of this article. However, it should be mentioned that there is a growing conviction that measurement of pulmonary arterial pressure may often be crucial in deciding upon the amount of lung tissue that may be surgically resected with safety. When the pulmonary capillary bed is reduced too far this creates such resistance to the flow of blood that higher right ventricular and pulmonary arterial pressures are required to maintain a normal volume of blood flow. A rise in these pressures during rest or mild exercise serves as a warning that further reduction in pulmonary vascular bed may lead to right ventricular failure.

Bronchospirometry

This is a method for simultaneous measurement of the function of individual lungs. The technic is described in detail elsewhere.[35,54,55] Separation of the air from the two lungs permits the following measurements: (1) partition of the tidal volume, minute volume and vital capacity between the two lungs; the right usually contributes 55 per cent and the left 45 per cent; (2) O_2 uptake for each lung; again the normal relation is 55:45 per cent; (3) calculation of the ventilatory equivalent for each lung.

When each lung breathes into a closed circuit spirometer system initially filled with O_2, it may be assumed that blood leaving the alveoli is maximally saturated with O_2 as a result of the high alveolar pO_2. Under these conditions reduced O_2 uptake on one side (in relation to its ventilation) is almost certainly due to reduced blood flow. Thus relative blood flow through the two lungs can be estimated from the slopes of the spirometer tracings.

The measurement of individual lung function by the technic of bronchial catheterization is used to predict the effect upon pulmonary function of permanent collapse therapy or surgical removal of lung tissue. As currently performed it has certain disadvantages: (1) the technic is difficult and requires a well trained team; (2) breathing through narrow, long tubes is abnormal and it is difficult to evaluate maximal breathing capacity and spirographic tracings; (3) the technic evaluates function of the better lung *in the presence of the lung to be removed*, and not that of the better lung existing alone; (4) it is contraindicated in the presence of tuberculous ulcerations of larynx, trachea or bronchi, high fever, recent hemoptysis and dyspnea; and (5) in patients with abundant secretions it is usually not possible to obtain satisfactory records. When bronchospiro-

metry cannot be done, some idea of individual lung function may be obtained from careful physical examination and fluoroscopy.

CONCLUSIONS

The value and limitations of some commonly used pulmonary function tests have been presented. There is no single test by which all aspects of pulmonary function can be evaluated and no magic number which serves as a sharp dividing line between health and pulmonary disability. However, significant contributions to the diagnosis and prognosis of cardiopulmonary disease may be made by thoughtful interpretation of data derived from a variety of physiologic tests.

REFERENCES

1. Baldwin, E. DeF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
2. Baldwin, E. DeF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. II. A study of thirty-nine cases of pulmonary fibrosis. *Medicine*, 28: 1, 1949.
3. Baldwin, E. DeF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 201, 1949.
4. Baldwin, E. DeF., Harden, K. A., Greene, D. G., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. IV. A study of 16 cases of large pulmonary air cysts or bullae. *Medicine*, 29: 169, 1950.
5. Bateman, J. B. Studies of lung volume and intrapulmonary mixing. Nitrogen clearance curves: apparent respiratory dead space and its significance. *J. App. Physiol.*, 3: 143, 1950.
6. Birath, G. Lung volume and ventilation efficiency. *Acta med. Scandinav., suppl.*, 154: 1–215, 1944.
7. Bloomer, W. E. The application of tests of respiratory physiology for the clinical evaluation of pulmonary pathology. *Yale J. Biol. & Med.*, 20: 135, 1947.
8. Christie, R. V. The lung volume and its subdivisions. *J. Clin. Investigation*, 11: 1099, 1932.
9. Christie, R. V. The elastic properties of the emphysematous lung and their clinical significance. *J. Clin. Investigation*, 13: 295, 1934.
10. Comroe, J. H., Jr. and Botelho, S. The unreliability of cyanosis in the recognition of arterial anoxemia. *Am. J. M. Sc.*, 214: 1, 1947.
11. Comroe, J. H., Jr., Bahnson, E. R. and Coates, E. O. Mental changes occurring in chronically anoxemic patients during oxygen therapy. *J. A. M. A.*, 143: 1044, 1950.
12. Comroe, J. H., Jr. (Editor) Methods in Medical Research, vol. 2, p. 74. Chicago, 1950. Yearbook Publishers.
13. Comroe, J. H., Jr. The value of pulmonary function tests in the diagnosis of pulmonary disease. *Tr. & Stud., Coll. Physicians, Philadelphia*, 4th series, vol. 18, no. 2, 1950.
14. Comroe, J. H., Jr. and Fowler, W. S. Detection of uneven alveolar ventilation during a single breath of oxygen; a new test of pulmonary disease. *Am. J. Med.*, in press.
15. Cournand, A., Richards, D. W., Jr. and Darling, R. C. Graphic tracings of respiration in study of pulmonary disease. *Am. Rev. Tuberc.*, 40: 487, 1939.

15*a*. Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Discussion of a physiological classification and presentation of clinical tests. *Am. Rev. Tuberc.*, 44: 26, 1941.

16. Cournand, A., Baldwin, E. DeF., Darling, R. C. and Richards, D. W., Jr. Studies on intrapulmonary mixture of gases: IV. Significance of pulmonary emptying rate and simplified open circuit measurement of residual air. *J. Clin. Investigation*, 20: 681, 1941.
17. Crehan, E. L., Kennedy, R. L. J. and Wood, E. H. A study of the oxygen saturation of arterial blood of normal newborn infants by means of a modified photo-electric oximeter: preliminary report. *Proc. Staff Meet., Mayo Clin.*, 25: 392, 1950.
18. Darling, R. C., Cournand, A. and Richards, D. W., Jr. Studies on intrapulmonary mixture of gases: III. Open circuit method for measuring residual air. *J. Clin. Investigation*, 19: 609, 1940.
19. Douglas, J. C. and Edholm, O. G. Measurement of saturation time and saturation tension with Millikan oximeter, in subjects with normal pulmonary function. *J. App. Physiol.*, 2: 307, 1949.
20. Dripps, R. D. and Comroe, J. H., Jr. The respiratory and circulatory response of normal man to inhalation of 7.6 and 10.4 per cent O_2 with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO_2 and maximal voluntary hyperventilation. *Am. J. Physiol.*, 149: 43, 1947.
21. Fenn, W. O. Mechanics of respiration. *Am. J. Med.*, 10: 77, 1951.
22. Fowler, W. S. and Blakemore, W. S. Lung function studies: VII. The effect of pneumonectomy on respiratory dead space. *J. Thoracic Surg.*, in press.
23. Fowler, W. S. Lung function studies: II. The respiratory dead space. *Am. J. Physiol.*, 154: 405, 1948.
24. Fowler, W. S. Methods in Medical Research, vol. 2, p. 226. Chicago, 1950. Yearbook Publishers.
25. Fowler, W. S. Lung function studies: III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J. App. Physiol.*, 2: 283, 1949.
26. Fowler, W. S., Cornish, E. R., Jr. and Kety, S. S. Measurement of alveolar ventilatory components. *Am. J. M. Sc.*, 220: 112, 1950.
27. Gaensler, E. A. Ventilatory tests in bronchial asthma. *J. Allergy*, 21: 232, 1950.
28. Gaensler, E. A. Air velocity index. *Am. Rev. Tuberc.*, 62: 17, 1950.

29. Gilson, J. C. and Hugh-Jones, P. The measurement of the total lung volume and breathing capacity. *Clin. Sc.*, 7: 185, 1949.
30. Goggio, A. F. The abnormal physiology of chronic pulmonary emphysema. *New England J. Med.*, 231: 672, 1944.
31. Gray, J. S., Barnum, D. R., Matheson, H. W. and Spies, S. N. Ventilatory function tests. I. Voluntary ventilation capacity. *J. Clin. Investigation*, 29: 677, 1950.
32. Greifenstein, F., King, R. M., Latch, S. S. and Comroe, J. H., Jr. Pulmonary function in elderly normal subjects. In press.
33. Keys, A. O_2 saturation of venous blood in normal human subjects. *Am. J. Physiol.*, 124: 13, 1938.
34. Kountz, W. B. and Alexander, H. L. Emphysema. *Medicine*, 13: 251, 1934.
35. Leiner, G. C. and Liebler, J. B. The technique of bronchospirometry. *Dis. of Chest*, 17: 578, 1950.
36. Maier, H. C. (Chairman) Report of the Sub-Committee on Pulmonary Function Tests, American Trudeau Society. *Am. Rev. Tuberc.*, 62: 451, 1950.
37. Matheson, H. W., Spies, S. N., Gray, J. S. and Barnum, D. R. Ventilatory function tests. II. Factors affecting the voluntary ventilation capacity. *J. Clin. Investigation*, 29: 682, 1950.
38. Matheson, H. W. and Gray, J. S. Ventilatory function tests. III. Resting ventilation, metabolism and derived measures. *J. Clin. Investigation*, 29: 688, 1950.
39. Mills, J. N. Variability of the vital capacity of the normal human subject. *J. Physiol.*, 110: 76, 1949.
40. Mills, J. N. The influence upon the vital capacity of procedures calculated to alter the volume of blood in the lungs. *J. Physiol.*, 110: 207, 1949.
41. Osher, W. J. Change of vital capacity with the assumption of the supine position. *Am. J. Physiol.*, 161: 352, 1950.
42. Pappenheimer, J. Standardization of definitions and symbols in respiratory physiology. *Federation Proc.*, 9: 602, 1950.
42*a*. Proctor, D. F. and Hardy, J. B. Studies of respiratory air flow. *Bull. Johns Hopkins Hosp.*, 85: 253–280, 1949.
43. Rahn, H. A concept of mean alveolar air and the ventilation-blood flow relationships during pulmonary gas exchange. *Am. J. Physiol.*, 158: 21, 1949.
44. Rahn, H., Fenn, W. O. and Otis, A. B. Daily variations of vital capacity, residual air and expiratory reserve including a study of the residual air method. *J. App. Physiol.*, 1: 725, 1949.
45. Riley, R. L. and Cournand, A. 'Ideal' alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J. App. Physiol.*, 1: 825, 1949.
46. Riley, R. L. Pulmonary gas exchange. *Am. J. Med.*, 10: 210, 1951.
47. Robertson, J. S., Siri, W. E. and Jones, H. B. Lung ventilation patterns determined by analysis of nitrogen elimination rates; use of the mass spectrometer as a continuous gas analyzer. *J. Clin. Investigation*, 29: 577, 1950.
48. Singer, R. B. and Hastings, A. B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine*, 27: 223, 1948.
49. Spain, D. M. Patterns of pulmonary fibrosis as related to pulmonary function. *Ann. Int. Med.*, 33: 1150, 1950.
50. Stephen, C. R. The influence of posture on mechanics of respiration and vital capacity. *Anesthesiology*, 9: 134, 1948.
51. Warring, F. C., Jr. Simple tests of ventilatory function for use in the sanatorium or clinic. *Am. Rev. Tuberc.*, 60: 149, 1949.
52. West, H. F. Clinical studies on respiration: VI. Comparison of various standards for normal vital capacity of lungs. *Arch. Int. Med.*, 25: 306, 1920.
53. Wood, E. H. Oximetry, in Glasser, O. (ed.) Medical Physics, Vol. 2. Chicago, 1950. Yearbook Publishers, Inc.
54. Wright, G. W. and Michelson, E. Bronchospirometry, in Methods in Medical Research, vol. 2, p. 82. Chicago, 1950. Yearbook Publishers, Inc.
55. Wright, G. W. and Woodruff, W. Bronchospirography. *J. Thoracic Surg.*, 11: 278, 1942.
56. Wright, G. W. Disability evaluation in industrial pulmonary disease. *J. A. M. A.*, 141: 1218, 1949.
57. Wright, G. W., Filley, G. F., Proemmel, D., Princi, F. Place, R. and Grinnell, R. Observations concerning the pathological physiology underlying exertional dyspnea in the disease "granulomatosis occurring in beryllium workers." In Symposium on Military Physiology, National Military Establishment Research and Development Board, 1947.

Roentgenographic Methods in Pulmonary Disease*

ABRAHAM G. COHEN, M.D. AND ABRAHAM GEFFEN, M.D.
New York, New York

THE standard routine roentgenogram of the chest (hereafter referred to as a plain film) is a postero-anterior view in an erect position with the breath held in deep inspiration. To obtain a routine chest film of good technical quality the following factors are used: tube-film distance of 6 feet, exposure time not exceeding one-tenth second, total exposure of 10 milliampere-seconds (which results in the optimum average film density) and 60 to 90 peak kilovoltage, depending upon the thickness of the chest.

A certain appearance of the plain chest roentgenogram has come to be known as normal or negative. This implies that there is no demonstrable abnormality in appearance and position of the lung fields, heart, mediastinal structures, bony thorax and diaphragm. The roentgenographic appearance of the normal chest is influenced by the age, sex and constitutional build of the individual. These physiologic variations, as well as definite pathologic changes, cannot always be recognized with certainty Competent observers may interpret differently roentgenographic findings which are on the borderline between normal and abnormal. The appearance of the plain chest roentgenogram in health and disease is very adequately considered in many textbooks and is not the subject of this article.[1–5]

The plain film has two main limitations. In the first place a negative film does not completely exclude the possibility of an intrathoracic disease for the following reasons: (1) Many lesions, particularly of the bronchi, do not cause roentgenographic abnormalities. (2) Lesions in the early phase of certain diseases, for example miliary tuberculosis, fail to cast shadows until they have reached a certain size. (3) Significant lesions of small extent may be obscured by the heart and great vessels, diaphragm or bony structures.

A second limitation is the fact that the plain film, although indicative of disease, often provides insufficient information for the following reasons: (1) The single plane fails to demonstrate the true three dimensional character of a lesion. (2) In extensive or multiple lesions denser shadows may obscure portions of the lesions. (3) The motion of various structures and its effects cannot be observed. The scope of the plain film in differential diagnosis is therefore often limited. Moreover, in the case of complex diseases such as tuberculosis, with its great variety of coexisting natural and induced pathologic changes, the plain film often fails to satisfy the requirements of modern therapy for detailed information.

Fortunately, many additional technics are now available which serve at least partially to overcome these limitations.[6,7] It is the purpose of this article to enumerate these special methods and to indicate the situations in which each of them may be applied to great advantage.

POSITIONING

Lateral and Oblique Views.[8,9] In the case of a unilateral lesion a lateral view is taken with the affected side closest to the film. An oblique view occasionally may provide additional information. In the case of bilateral

* From the Departments of Medicine and Radiology of the Beth Israel Hospital, New York, N. Y.

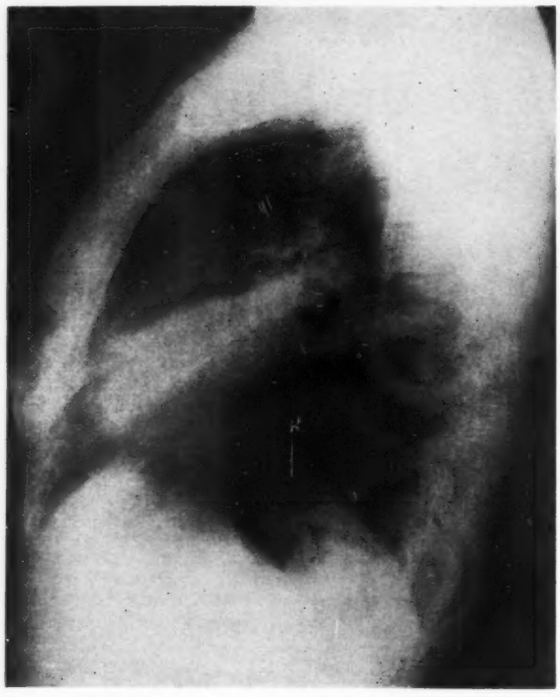
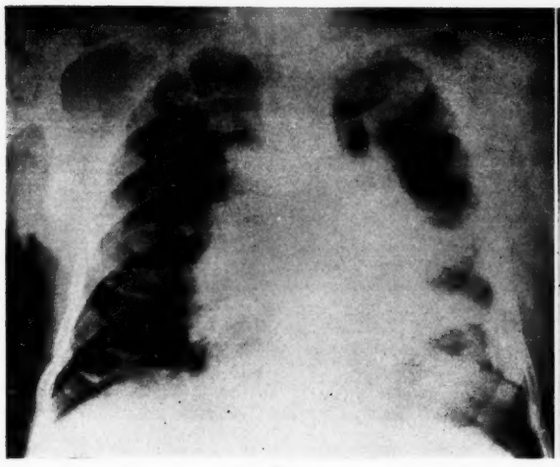


FIG. 1. Left lateral view showing atelectasis of the lingula of the left upper lobe in a case of broncholithiasis. Postero-anterior view showed an indefinitely outlined density in the left mid-lung field. A subsequent bronchogram showed an abrupt termination of the lingula bronchus 2 cm. from its origin.

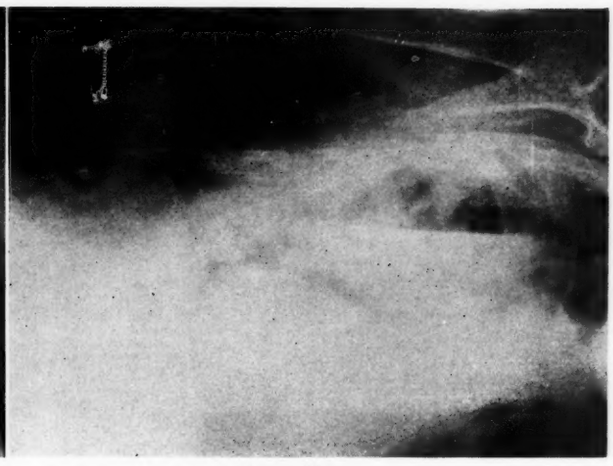
lesions both left and right anterior oblique projections (anterior chest closest to film) are required. These views are valuable in many ways. (1) While the postero-anterior view localizes a lesion in only one (frontal) plane, the lateral view does this in an additional (sagittal) plane. Thus by means of the two views the lesion can be localized accurately. In the case of pulmonary lesions the exact lobe or segment thereof which is involved can be determined. (Fig. 1.) This is of the utmost importance both in diagnosis and therapy. The position of a mediastinal lesion in the sagittal plane can be determined. In the case of tumors determination of the type is thus facilitated. For example, teratomas usually are anterior while neurogenic tumors are posterior. Precise localization in two planes is essential prior to aspiration of encapsulated pleural effusions. (2) The appearance of a lesion in the lateral view supplements that of the postero-anterior view so that a more complete picture of its size, shape and structure is obtained. In the case of some lesions such as interlobar effusion or shrunken right middle lobe the appearance in the lateral view may be characteristic. (3) Lateral and oblique views may disclose lesions which are obscured by the heart and great vessels, diaphragm, bony structures or involved portions of the lung or pleura. The heart shadow often may hide a lesion of the left lower lobe of the lung. Lesions such as substernal thyroid, thymic tumors and pneumomediastinum are at least partially obscured by the sternum, spine and mediastinal structures and always are seen best in a lateral view. For the same reason enlarged mediastinal lymph nodes are seen best in an oblique view. Very small pleural effusions may be hidden by the diaphragm. In artificial pneumothorax (for tuberculosis) the presence and position of adhesions may be obscured by the partially collapsed lung. (4) These views aid in the differentiation of mediastinal from pulmonary lesions. (5) The complete contour of the diaphragm can be determined. (6) The position of the interlobar fissures can be ascertained. Displacement of a fissure is evidence of hyper- or hypo-aeration of a pulmonary lobe.

Supine, Trendelenburg and Lateral Decubitus Positions. In the supine position the patient lies flat on his back on the table. The cassette is placed beneath him and the rays are directed downward (anteroposterior). The Trendelenburg position is similar except that the table is tilted 30 to 45 degrees so tha the patient's head is lower than his feet. In the lateral decubitus (recumbent) position the patient lies on his side. The cassette is held vertically and either a postero-anterior or an anteroposterior view is taken. It is customary to designate this position right or left according to the dependent side.

These positions are valuable because advantage is taken of the fact that fluid shifts with change in position unless it is very thick or loculated. (1) *Simple hydrothorax:* Rigler[10,11] has demonstrated that in a plain film the presence of at least 500 cc. of fluid is required before a shadow is visi-



2



3

FIG. 2. Anteroposterior view, with patient in Trendelenburg position, after substitution of air for the original pleural effusion. A case of hypernephroma complicated by pleural metastases and effusion. This view shows metastatic pleural deposits at the apex, directly above the diaphragm and along the lateral chest wall. These were not seen clearly in a plain film taken after thoracentesis.

FIG. 3. Postero-anterior view, with patient in right lateral decubitus position, in a case of left encapsulated pyopneumothorax. By means of the shift of the fluid level the apicocaudal extent of the empyema cavity was determined.

ble. However, in either the supine or lateral decubitus (affected side down) positions as little as 100 to 200 cc. is detectable. In cases in which the plain film shows a shadow suggestive of a pleural effusion it may be necessary to differentiate between fluid and thickened pleura. This can be accomplished by demonstrating, in the case of fluid, a shift in the shadow with a change to either of these positions. By means of the supine, Trendelenburg or decubitus (unaffected side down) positions it is possible to expose portions of the lower lobe and diaphragm obscured by fluid. (Fig. 2.) (2) *Hydropneumothorax:* When air is also present, fluid shifts very readily and the aforementioned maneuvers may be accomplished with even more satisfactory results. In the case of an encapsulated pyopneumothorax the complete apicocaudal extent of the pocket can be determined by means of the shift of the fluid level with a change to the lateral decubitus position. (Fig. 3.)

Tilting. A postero-anterior view is taken but with the patient tilted to either side. A fluid level within a pulmonary or pleural cavity denoting the presence of both air and fluid then will shift to a new horizontal position. By this method fluid levels can be differentiated from other linear horizontal shadows. The demonstration of a fluid level is important because it confirms the presence of a pulmonary cavity. In a pneumothorax the presence of fluid may be clinically significant. By means of tilting a pleural fluid level can be differentiated from a flattened diaphragm.

A pulmonary cavity, particularly in tuberculosis, may be entirely empty of fluid and difficult to visualize, especially when the chest wall is deformed as the result of previous surgery. According to the method of Leon, Green and Serbst[12] patients in such cases are given codeine and phenobarbital before retiring and are advised not to expectorate on the following morning. Roentgenograms taken very early that day both in the conventional position and with the patient tilted often show fluid levels.

Lordotic Position. (1) *Anteroposterior view:*[13,14] The patient stands as far forward as possible and leans backward so that his shoulders rest against the cassette. An anteroposterior view is then taken. This enables one to visualize small lesions in the upper portions of the lungs which on the plain film may be obscured by the clavicles and upper ribs. The most important application is in tuberculosis. When this disease

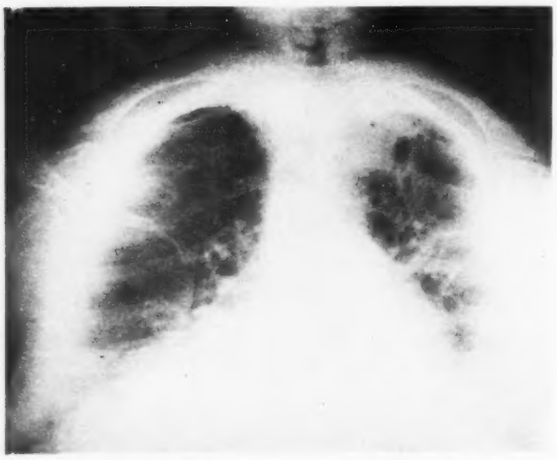


FIG. 4. Lordotic position, anteroposterior view, showing a cavity in the left upper lobe. A plain film showed an infiltration without cavitation which was obscured by the clavicle and upper ribs.

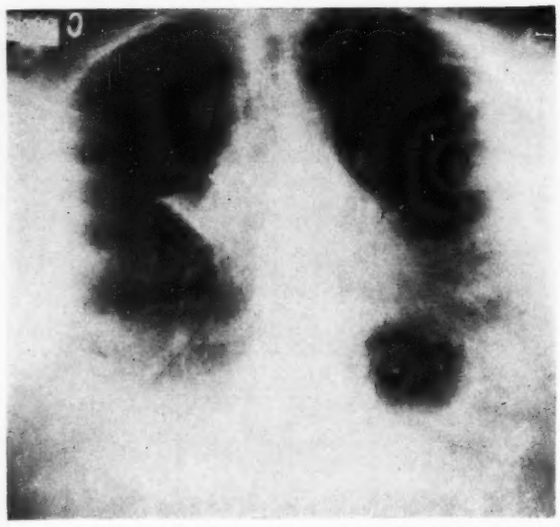


FIG. 5. Lordotic position, postero-anterior view, showing the characteristic triangular shadow of a shrunken right middle lobe. A plain film showed a small area of infiltration in the right lower lung field mesially.

is suspected a negative report should not be rendered on the basis of a plain film alone. Small hidden cavities may be revealed in the lordotic position. (Fig. 4.) This view also is useful for the detection of other lesions, particularly tumors, which are situated in the apical regions. (2) *Postero-anterior view:*[15,16] The positioning is the same as before except that the front of the chest instead of the back is closest to the film. This view is excellent for the demonstration of a shrunken right middle lobe which assumes a characteristic triangular appearance. (Fig. 5.)

Stereoscopic Views. In addition to the routine view, while the patient is still holding his breath in deep inspiration, the tube is rapidly shifted in position in the vertical plane by means of automatic devices; another cassette replaces the first and a second exposure is made. The two films then can be viewed stereoscopically. The depth perception provides more definite localization of abnormal shadows. The method is useful in limited instances but is not recommended as a routine procedure.

PHYSIOLOGIC MODIFICATIONS

Expiration.[17] In some diseased conditions a film taken in expiration shows important differences from that taken in inspiration. (1) In obstructive emphysema of an entire lung due to partial bronchial obstruction the mediastinal shadow is located in the midline in inspiration (and therefore normal in the plain film) but shifts to the unaffected side in expiration. On the other hand, in atelectasis the shift is to the affected side in inspiration, with a return to the midline in expiration. (2) In obstructive emphysema of a segment, lobe or lung there is an increased radiolucency of the affected part which is easy to overlook, particularly on a dark film. There is also a convexity of the bordering fissure. Deep expiration intensifies this radiolucency and also increases the convexity of the fissure.[18] The demonstration of obstructive emphysema is of great value in the detection of partial bronchial obstruction. (3) Expiration increases the relative size of a pneumothorax. It is therefore of value in detecting a shallow pneumothorax which is not revealed by the plain film. (4) In the presence of a pneumothorax under tension the mediastinum often shifts to the opposite side during expiration. The compression of the opposite lung may give a deceptive appearance of disease. (5) The shadow caused by arteriovenous fistula (hemangioma) of the lung increases in size with inspiration and decreases with expiration.[19,20] (6) The normal diaphragm

descends with inspiration and ascends with expiration. The reverse occurs (paradoxic motion) in diaphragmatic paralysis due to phrenic nerve involvement and often in complete eventration of the diaphragm. In partial eventration the affected portion alone may move paradoxically. Old or recent pleuritis may result in fixation of the diaphragm. Abnormalities of diaphragmatic motion are better demonstrated fluoroscopically than roentgenographically.

Breathing at a Constant Intra-alveolar Pressure. This is accomplished by breathing against a water manometer through a rubber tube held in the mouth until a specified level is reached. Westermark[21] has described, in certain diseases, considerable differences between plain inspiration films and those taken in this manner. This method has not achieved extensive application, at least in this country.

PENETRATION TECHNICS

Varying Exposure. Radiologists and internists vary in their preference for lighter and darker films. Undoubtedly, one or the other will produce better results in different situations. (1) Slightly less penetration may sometimes bring out thin-walled cysts, shallow pneumothoraces or small tuberculous or other infiltrations. (2) An overpenetrated (overshot) film is useful in demonstrating lesions which are obscured by other shadows.[22,23] For this purpose the use of the Potter-Bucky diaphragm is preferable.

Potter-Bucky Diaphragm. (1) By use of the diaphragm a dense shadow caused by a deformity of the chest wall (thoracoplasty, etc.), pleural effusion, thickened pleura, tumor mass or consolidated lung can be penetrated to some extent. Hidden cavities, calcifications and masses may thus be revealed. (2) The ribs may become involved in pulmonary diseases such as carcinoma, tuberculosis or fungus infection. On the other hand, primary diseases of the rib may simulate pulmonary diseases. In the demonstration of rib pathology the Potter-Bucky film is essential. (Fig. 6.)

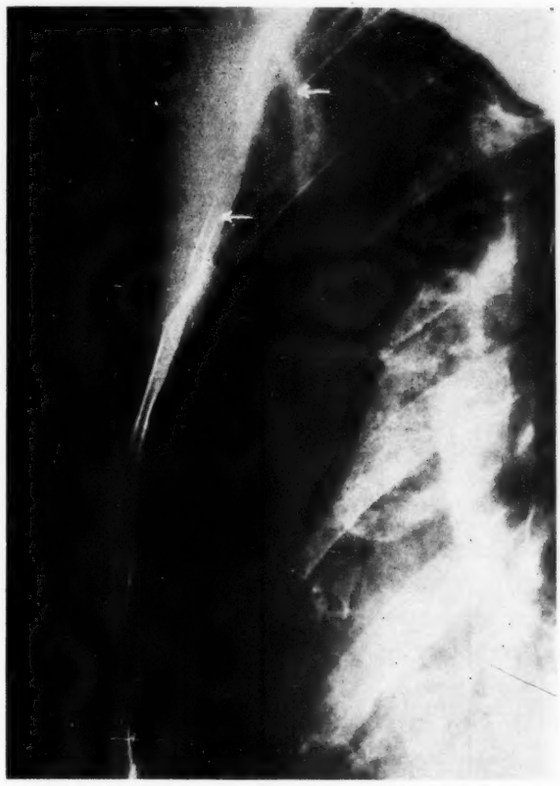
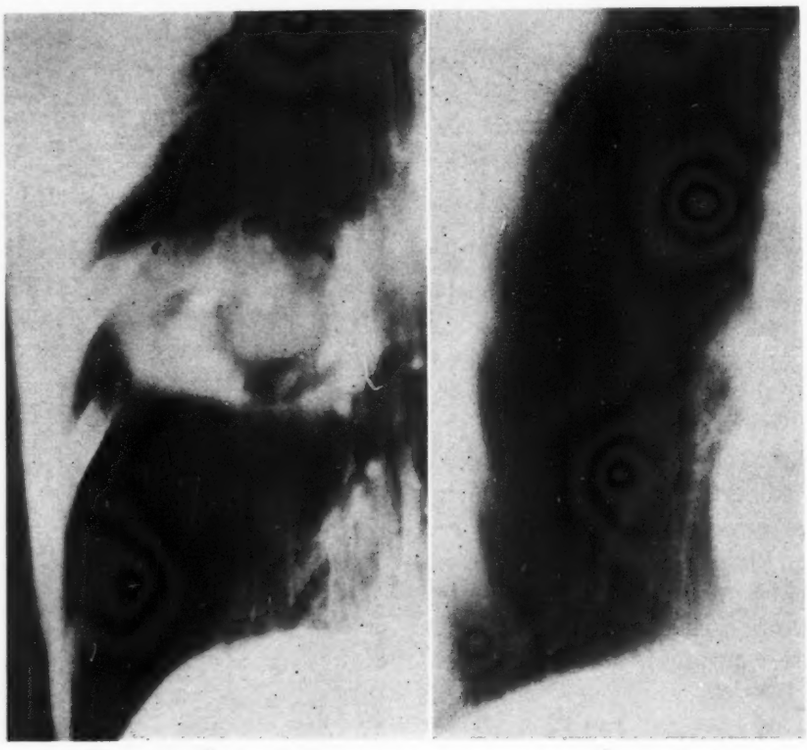


FIG. 6. Oblique view, using Potter-Bucky diaphragm, showing destruction of rib (arrows) and also a soft tissue mass in a case of multiple myeloma. A plain film demonstrated the mass which was located in the periphery of the right lung. Fluoroscopy determined its location and guided the positioning for the special view.

*Body-section Roentgenography** (*Planigraphy, Laminagraphy, Tomography*).[24–26] This is the technic of making roentgenograms which show detail in the images of structures lying in a certain predetermined plane of tissue while blurring detail in the images of structures of other planes. Thus any specific plane of the body can be selected to be visualized on the film as if an anatomic section had been made through that plane. Tomograms are produced by movement of the film during exposure in a direction reciprocal and proportional to a simultaneous movement of the tube. Tomograms may be taken in the postero-anterior, anteroposterior or lateral positions, in each case with the patient lying horizontally on the table. The specific lesion for special

* The term "planar roentgenography" recently has been introduced.



7 8

FIG. 7. Body-section roentgenogram, anteroposterior, 7 cm. from posterior chest wall, showing a cavity with an irregular growth within it, all within a large mass (carcinoma). These findings corresponded accurately to the changes within the resection specimen.

FIG. 8. Body-section roentgenogram, postero-anterior, 8.5 cm. from anterior chest wall, showing a small area of calcification within a homogeneous peripheral nodule. The diagnosis of a healed tuberculous focus ("tuberculoma") was thus indicated. A plain film did not show calcification.

study must be localized by plain, oblique and lateral films or, if necessary, by fluoroscopy prior to tomography so that the precise level and interval of the planes to be visualized are predetermined. (1) This method is invaluable for the demonstration of tuberculous and other cavities which are obscured by overlying shadows in plain films.[27–29] Vertical tomography, which recently has been developed, is of additional value because it permits visualization of fluid levels.[30] (2) It is very useful in the diagnosis of pulmonary neoplasms.[31–33] Impingement of the tumor upon the bronchial lumen can be demonstrated. In a large shadow that portion which is due to atelectasis may be delineated from that portion due to the tumor itself. Eccentric or irregularly shaped areas of breakdown within a mass are highly suggestive of carcinoma. (Fig. 7.) Mediastinal lymph nodes can be demonstrated. (3) Calcifications and opaque foreign bodies obscured by other shadows can be demonstrated and localized. (Fig. 8.) (4) Post-inflammatory bronchial strictures are demonstrable.

USE OF CONTRAST SUBSTANCES

Gas. This is an excellent contrast medium when introduced into various body cavities. Atmospheric air is usually satisfactory. (1) *Pneumothorax:*[34] Several hundred cubic centimeters of air are introduced directly into an unoccupied pleural cavity as in the treatment of tuberculosis. If fluid is present, it is withdrawn and replaced with air. Caution should be observed in the case of individuals with emphysema or cystic disease or with limited respiratory reserve. Tumors of the visceral pleura or of the lung

may be differentiated from those of the thoracic cage or parietal pleura. The former separate from the chest wall with the collapsed lung while the latter do not. Indefinite nodular shadows in the plain film which suggest carcinomatosis of the pleura are outlined conspicuously by means of pneumothorax. (Fig. 2.) (2) *Pneumoperitoneum:* The introduction of only 600 to 800 cc. of air is usually sufficient. Caution must be observed in individuals who have had previous abdominal operations. Postero-anterior and lateral films are taken in the erect position. Normally, air will appear beneath and elevate both leaves of the diaphragm. This fact is applicable in the differential diagnosis of dense shadows in the lower chest which may represent elevation of the diaphragm (eventration or phrenic paralysis), fluid between the diaphragm and lung (infrapulmonary effusion) or lesions in the lower portion of the lung. In such situations the position of the diaphragm in relation to the shadow is readily determined by means of pneumoperitoneum. (Fig. 9.)[35,36] The procedure differentiates eventration from diaphragmatic hernia; the air causes the diaphragm to separate from the abdominal viscera in eventration but not in hernia.[37,38] (3) *Gas bubble in the stomach:* Following the administration of a Seidlitz powder, citrocarbonate or club soda the stomach becomes distended with gas. The position of the left diaphragm is thus outlined as by pneumoperitoneum.

Iodized Oil. This is a combination of iodine and vegetable oil which is radiopaque. (1) *Bronchography:*[39–47] The oil is introduced into the bronchial tree and outlines the various branches. There are numerous technics for the introduction of the oil and also for positioning the patient in taking the roentgenograms. For infants and young children special methods have been devised which often include a general anesthesia. The reader is referred to the original articles for details. The authors do not wish to express preference for any one technic but believe that it is desirable to master by practice whichever one is used. The selection of cases for bronchography requires discretion since the method is not entirely innocuous.[48] The iodized oil may remain in the alveoli and obscure roentgenographic detail for long periods of time. Serious pneumonic reactions may occur. The respiratory reserve may be diminished to the extent that urgent surgery must be delayed. The interpretation of bronchograms requires familiarity with the detailed anatomy of the bronchial tree.[49–51] The indication *par excellence* for bronchography is bronchiectasis. In this disease plain films are often entirely normal or at most show suspicious changes whereas bronchograms readily reveal the dilated bronchi. (Fig. 10.) However, it no longer is adequate merely to demonstrate the presence of bronchiectasis in some portion of the lung. Modern surgery requires a complete mapping out of both lungs bronchographically so that the exact extent of the disease in terms of lobes and segments is predetermined. By bronchography, obstruction of the smaller bronchi can be demonstrated. The most important application of this is in the diagnosis of bronchogenic carcinomas which lie beyond the view of the bronchoscopist; obstruction from other causes also can be demonstrated. (2) Iodized oil can be introduced into fistulas between the chest wall and the pleura or lung. The size and configuration of tuberculous cavities (after cavernostomy operation) or residual empyemas can thus

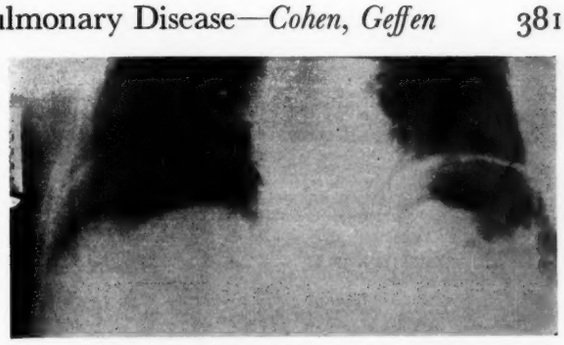


FIG. 9. Postero-anterior view, with patient in erect position, using Potter-Bucky diaphragm after induction of pneumoperitoneum, showing air under the right leaf of the diaphragm. A plain film showed a rounded density projecting from the medial half of the right diaphragm which changed in size during respiration, being largest in inspiration. Pneumoperitoneum proved that the mass represented a portion of the liver beneath a partially eventrated right diaphragm.

FIG. 10. Bronchogram, postero-anterior view, showing saccular bronchiectasis of the right lower lobe. A plain film was not remarkable.

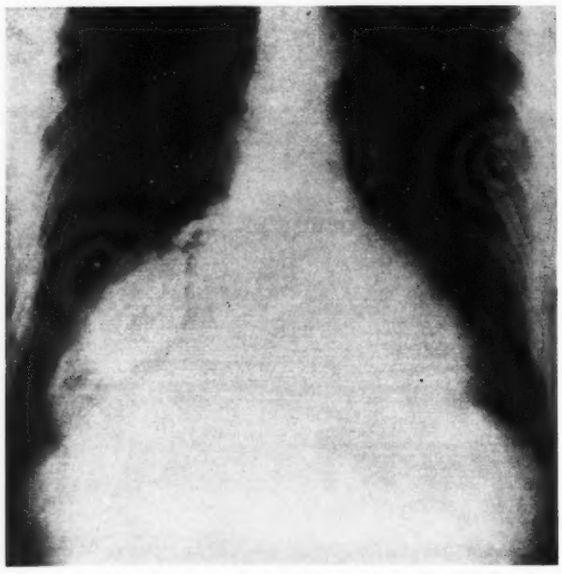


FIG. 11. Postero-anterior view, using Potter-Bucky diaphragm, after administration of barium by mouth The barium is seen in the stomach which is located within the right chest, thus indicating a diaphragmatic hernia. A plain film showed a density in the right lower chest extending outward from the cardiac border.

be determined. (3) Rabin[52] has described a spot technic for the precise localization of pulmonary abscesses prior to surgical drainage. A mixture of 0.2 cc. each of iodized oil and methylene blue is injected into an intercostal muscle directly over an abscess. By means of films taken in various positions the relationship of the spot to the abscess can be determined. The methylene blue then serves to guide the surgeon. (4) By means of iodized oil introduced into the esophagus a tracheo- or broncho-esophageal fistula can be demonstrated. Barium is contraindicated for this purpose.

Angiocardiography.[53–56] Visualization of the cardiac chambers and great vessels is obtained after intravenous injection of a suitable radiopaque substance. Special technical devices for rapid successive exposures are available. Although the procedure was devised primarily for the study of diseases of the cardiovascular system, it has been found to be useful in the study of thoracic diseases. (1) It is often impossible to differentiate an aortic aneurysm from a mediastinal tumor by ordinary methods. The presence or absence of pulsation is not conclusive. By angiocardiography an aneurysm usually is filled by the contrast substance whereas a tumor never is filled. (2) The position of mediastinal masses, including benign tumors and lymphoblastomas, in relation to the great vessels can be determined. (3) Characteristic changes are observed in arteriovenous fistula (hemangioma) of the lung.[57,58] (4) In pulmonary carcinoma alterations in the vascular pattern have been observed which are of some value in differential diagnosis.[59] These observations recently have been extended so as to include criteria for the probable inoperability of these tumors.[60]

Barium. (1) *Esophagram:* Primary carcinoma of the esophagus occasionally produces a mediastinal shadow (due to nodes or infection) which must be differentiated from a primary pulmonary or mediastinal lesion. A barium study will demonstrate the esophageal lesion. A markedly dilated esophagus resulting from achalasia (cardiospasm) may cast a curved longitudinal shadow to the right of the heart border on the plain film. Barium will demonstrate the true character of the lesion.[61] It has been

stated that distortion of the barium-filled esophagus caused by involved lymph nodes is evidence for the inoperability of bronchogenic carcinoma. This has not been confirmed by our own studies. (2) *Stomach and colon studies:* The presence of diaphragmatic hernia or eventration can be demonstrated readily by the presence of the barium-filled abdominal viscera within the thorax. (Fig. 11.)

FLUOROSCOPY[62]

Due to the impairment of visual acuity and intensity discrimination at the low brightness levels that obtain during clinical fluoroscopy, even an experienced examiner after complete dark adaptation will not see certain small pulmonary lesions. Therefore, a plain roentgenogram is always essential. Fluoroscopy does serve as a supplement to roentgenography by its guidance for the selection of additional views. However, its greatest value lies in the fact that the motion of various structures can be observed directly. Many of these points already have been considered in the other sections and will only be noted here. (1) Normal and abnormal diaphragmatic motion can be demonstrated best by extremes of inspiration and expiration, using the Müller experiment (sniffing against a closed glottis) and the Valsalva experiment (straining against a closed glottis), respectively; (2) mediastinal shift with inspiration and expiration in atelectasis and obstructive emphysema of the lung; (3) shifting fluid level in pulmonary and pleural cavities with change of position; in a left hydropneumothorax undulation of the fluid level synchronously with the heart beat is observed occasionally; (4) variation in the volume of a lung collapsed by pneumothorax (in tuberculosis) during respiration; increase in the relative size of a pneumothorax during expiration; (5) the presence of vascular pulsation synchronous with cardiac systole is of some value in differentiating aneurysmal enlargement of vascular structures from tumors; however, the findings must be interpreted with caution since the pulsation of a normal aorta or other large artery can be transmitted to a neighboring tumor; (6) rise of the shadow of a substernal thyroid with swallowing; (7) variation in the size of the shadow of an arteriovenous fistula (hemangioma) of the lung during respiration; (8) pulmonary function; a rough estimate can be made of the relative percentage of ventilation carried on by each lung.[63]

SUMMARY

To overcome the limitations of the routine chest roentgenogram and to supplement the information derived from it many aditional roentgenographic technics are now available. The authors have grouped these methods as follows: (1) positioning, (2) physiologic modifications, (3) penetration technics, (4) use of contrast substances and (5) fluoroscopy.

The application of these methods in the study of pulmonary disease is indicated.

REFERENCES

1. Rabin, C. B. in Golden, R. Diagnostic Roentgenology. New York, 1936. Thos. Nelson and Sons.
2. Rigler, L. G. The Chest. Chicago, 1946. The Year Book Publishers.
3. Rubin, E. H. Diseases of the Chest. Philadelphia, 1947. W. B. Saunders Co.
4. Snow, W. Principles in Roentgen Study of the Chest. Springfield, Ill., 1946. C. C Thomas.
5. Zimme, E. A. Die Durchleuchtungstechnik der Thoraxorgane. Basel, 1946. Benno Schwabe.
6. Zinitheo, C. J., Jr. Auxiliary techniques in chest roentgenography. *Am. Rev. Tuberc.*, 37: 14, 1938.
7. Rigler, L. G. The possibilities and limitations of roentgen diagnosis. *Am. J. Roentgenol.*, 61: 743, 1949.
8. Chapman, J. F. The value of the lateral exposure in the roentgen examination of the chest. *Radiology*, 10: 139, 1928.
9. Pierce, C. B. and Stocking, B. W. The oblique projection of the thorax. *Am. J. Roentgenol.*, 38: 245, 1937.
10. Rigler, L. G. Roentgen diagnosis of small pleural effusions. *J. A. M. A.*, 96: 104, 1931.
11. Rigler, L. G. Roentgenologic observations on the motion of pleural effusions. *Am. J. Roentgenol.*, 25: 220, 1931.
12. Leon, J. H., Green, H. and Serbst, C. A. Visualization of cavities in post-thoracoplasty lungs. *Dis. of Chest*, 7: 274, 1941.
13. Baum, F. and Black, L. T. The importance of the apical roentgenogram in pulmonary tuberculosis. *Am. Rev. Tuberc.*, 12: 228, 1925.

14. Bobrowitz, I. D. and Hurst, A. Minimal tuberculosis. Problems in roentgenologic interpretation. *Radiology*, 52: 519, 1949.
15. Robbins, L. L. and Hale, C. H. The roentgen appearance of lobar and segmental collapse of the lung. v. Collapse of the right middle lobe. *Radiology*, 45: 260, 1945.
16. Doig, A. J. Atelectatic bronchiectasis of the right middle lobe. *Tubercle*, 27: 173, 1946.
17. Korol, E. and Scott, H. A. The use of chest roentgenograms with breath held in expiration. *Am. J. Roentgenol.*, 31: 266, 1934.
18. Golden, R. Abnormally wide respiratory movement of lower lung structures. Roentgen evidence of obstructive emphysema. *Am. J. Roentgenol.*, 44: 325, 1940.
19. Lindgren, E. Roentgen diagnosis of arteriovenous aneurysm of the lung. *Acta Radiol.*, 27: 585, 1946.
20. Barnes, C. G., Fatti, L. and Pryce, D. M. Arteriovenous aneurysm of the lung. *Thorax*, 3: 148, 1948.
21. Westermark, N. Roentgen Studies of the Lungs and Heart. Minneapolis, 1948. University of Minnesota Press.
22. Rigler, L. G. The density of the central shadow in the diagnosis of intrathoracic lesions. *Radiology*, 32: 316, 1939.
23. Tager, S. N. Use of over-penetrated film technic in diagnosis of cavities. *Radiology*, 39: 389, 1942.
24. Andrews, J. R. and Stava, R. J. Planigraphy. II. Mathematical analyses of the methods, description of apparatus, and experimental proof. *Am. J. Roentgenol.*, 38: 145, 1937.
25. McDougall, J. B. Tomography. London, 1940. H. K. Lewis & Co.
26. Weinbren, M. A Manual of Tomography. London, 1940. H. K. Lewis & Co.
27. Rotach, F. Die Bedeutung der Tomographie bei der nicht-kavernösen Lungentuberkulose. *Schweiz. med. Wchnschr.*, 75: 1029, 1945.
28. Morgenstern, P., Carr, C. E. and Nalls, W. L. Evaluation of planigrams in pulmonary tuberculosis. *Am. J. Roentgenol.*, 62: 402, 1949.
29. Touraine, R. Remarques sur les possibilités et limites de la tomographie frontale dans l'étude de la tuberculose pulmonaire commune de l'adulte. *Poumon*, 5: 463, 1949.
30. Crombie, D. W. and Andrus, P. M. Vertical tomography of the thorax. *Am. Rev. Tuberc.*, 62: 170, 1950.
31. Frimann-Dahl, J. On the value of planigraphy in bronchial cancer. *Acta Radiol.*, 27: 99, 1946.
32. Rigler, L. G. and Merner, T. B. Planigraphy in the diagnosis of bronchogenic carcinoma. *Am. J. Roentgenol.*, 58: 267, 1947.
33. Andrews, J. R. and Turek, R. O. Planigraphy. III. An evaluation of the method in the diagnosis of cancer of the lower respiratory tract. *Am. J. Roentgenol.*, 58: 173, 1947.
34. Singer, J. J. Diagnostic pneumothorax. *Ann. Clin. Med.*, 4: 907, 1926.
35. Jones, D. B. Basal pleural fluid accumulations resembling elevated diaphragm. *Radiology*, 50: 227, 1948.
36. Rothstein, E. and Landis, F. B. Infrapulmonary pleural effusion simulating elevation of the diaphragm. *Am. J. Med.*, 8: 46, 1950.
37. Walton, H. J. Eventration of the diaphragm. *Am. J. Roentgenol.*, 11: 420, 1924.
38. Faulkner, W. B., Jr. Diaphragmatic hernia and eventration. *Am. J. Roentgenol.*, 45: 72, 1941.
39. Di Rienzo, S. Radiologic Exploration of the Bronchus. Springfield, Ill., 1949, C. C Thomas.
40. Field, C. E. Bronchography in children. *Lancet*, 2: 357, 1942.
41. Wishart, D. E. S. Bronchography in bronchiestasis in children. *Ann. Otol., Rhin. & Laryng.*, 56: 404, 1947.
42. Way, G. L. and James, G. C. W. General anaesthesia for bronchography in children. *Lancet*, 1: 1073, 1950.
43. Miller, J. B., Conyers, W. H., Jr. and Dinhoffer, N. A simple, safe bronchographic technique for children. *J. Pediat.*, 36: 721, 1950.
44. Slater, P. S. Bronchography, details of a simple method. *Quart. Bull., Sea View Hosp.*, 8: 47, 1946.
45. Poppe, J. K. A simple and practical method of obtaining complete bronchograms. *Am. Rev. Tuberc.*, 54: 104, 1946.
46. Zavod, W. A. Improved technique for bronchograms. *Am. J. Roentgenol.*, 55: 356, 1946.
47. Schmidt, H. W. A method of obtaining bilateral bronchograms. *Proc. Staff Meet., Mayo Clin.*, 23: 71, 1948.
48. Overholt, R. H. and Ramsey, B. H. Discretion in the use of bronchography. *Dis. of Chest*, 15: 745, 1949.
49. Jackson, C. L. and Huber, J. F. Correlated applied anatomy of the bronchial tree and lungs with a system of nomenclature. *Dis. of Chest.*, 9: 319, 1943.
50. Brock, R. C. The Anatomy of the Bronchial Tree. London, 1947. Oxford University Press.
51. The Thoracic Society. The nomenclature of bronchopulmonary anatomy. *Thorax*, 5: 222, 1950.
52. Rabin, C. B. A technique for the more precise localization of pulmonary abscess. *Am. J. Roentgenol.*, 46: 130, 1941.
53. Sussman, M. L. Angiocardiography. *Surg., Gynec. & Obst.*, 87: 349, 1948.
54. Dotter, C. T. and Steinberg, I. Clinical angiocardiography: a critical analysis of the indications and findings. *Ann. Int. Med.*, 30: 1104, 1949.
55. Abbott, O. A., Hopkins, W. A. and Leigh, T. F. The role of angiocardiography and venography in mediastinal and paramediastinal lesions. *J. Thoracic Surg.*, 18: 869, 1949.
56. Steinberg, I., Dotter, C. T. and Andrus, W. DeW. Angiocardiography in thoracic surgery. *Surg., Gynec. & Obst.*, 90: 45, 1950.
57. Duisenberg, C. E. and Arismendi, L. The angiocardiographic demonstration of pulmonary arteriovenous fistula. *Radiology*, 53: 66, 1949.
58. Grishman, A., Poppel, M. H., Simpson, R. S. and Sussman, M. S. The roentgenographic and angiocardiographic aspects of 1. aberrant insertion of pulmonary veins associated with interatrial septal defect and 2. congenital arteriovenous aneurysm of the lung. *Am. J. Roentgenol.*, 62: 500, 1949.

59. NEUHOF, H., SUSSMAN, M. L. and NABATOFF, R. A. Angiocardiography in the differential diagnosis of pulmonary neoplasms. *Surgery*, 25: 178, 1949.
60. DOTTER, C. T., STEINBERG, I. and HOLMAN, C. W. Lung cancer operability. Angiocardiographic study of fifty-three consecutive proved cases of lung cancer. *Am. J. Roentgenol.*, 64: 222, 1950.
61. HURST, A. and BASSIN, S. Mega-esophagus as a cause of mediastinal widening. *Am. J. Roentgenol.*, 52: 598, 1944.
62. HENNY, G. C. and CHAMBERLAIN, W. E. Fluoroscopy. In Glasser, O., Medical Physics, pp. 1292–1309. Chicago, 1944. The Year Book Publishers.
63. American Trudeau Society. Report of the subcommittee on pulmonary function tests. *Am. Rev. Tuberc.*, 62: 451. 1950.

Clinic on Psychosomatic Problems

Convalescence in a Patient with Permanent Neurologic Disability

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. LAURENS WHITE: S. H. (No. 290767), a forty-two year old unmarried woman, was admitted to the Neurosurgical Service of the Massachusetts General Hospital for consideration of partial sectioning of the anterior lumbar nerve roots to relieve intractible spasms of her leg muscles.

Her story goes back fourteen years when, following a respiratory infection, there was sudden onset of severe, knife-like pain in both lumbar regions with radiation along the distribution of the right sciatic nerve. The pain was not affected by coughing or sneezing and nothing relieved it save lying prone in bed. She was more inconvenienced than incapacitated by it but as the severity gradually increased, she came to a clinic a year later where lumbar puncture and myelograms failed to show any abnormality except a spinal fluid protein of 59 mg. per cent. She had several interviews with a psychiatrist and a diagnosis of hysteria was made. She returned home with the pain unchanged. During the next four years it increased in severity and she noted some pain in the left buttock and thigh.

She entered this hospital for the first time nine years ago and at that time a myelogram was reported to show slight protrusion of the intervertebral substance bilaterally at L5. A laminectomy was performed and some disc material removed but no note was recorded as to the presence of nerve compression. Spinal fusion was done at that time. After the operation she continued to complain of severe pain in the right sciatic distribution and ten weeks later a second laminectomy and fusion were performed with the removal of more disc material. After the second operation the pain shifted from the right side to the left and she was eventually sent home with considerable pain in the left sciatic area.

Two years later, because the pain was becoming unbearable, she returned for consideration of cordotomy. She had been taking increasing amounts of codeine in the months before admission. The only significant neurologic abnormality was absence of knee jerks and ankle jerks bilaterally. She was examined by two neurologists whose diagnosis was "hysteria." The psychiatrist who had seen her originally at the outside clinic, said that there was "no psychiatrically treatable disease" and advised cordotomy which was performed in two stages. Following this operation her pain was completely relieved for three years.

Four years ago she began to notice a "tight sensation" in her toes and soon there were uncontrolled contractions in the muscles of both lower extremities. The spasms made walking difficult and during that year she had several falls. Finally, she had a very bad fall which resulted in recurrence of back pain. X-ray of the spine showed separation of the fusion. Rest in bed at home was of no avail and she returned to this hospital twenty-six months ago. Neurologic examination showed findings consistent with the previously performed cordotomy. Further psychiatric evaluation by the same consultant resulted in the same opinion, namely, no significant emotional problems.

While in the hospital, it was noted that she had frequency of urination with some loss of urinary control, resulting in dribbling but no real bed-wetting. Further operative procedures were decided against and she was sent home essentially unchanged.

The tightness of the leg muscles increased with augmentation of gait disturbance. The spasms were uncomfortable though not actually painful and during the next year increased in severity. Finally, she entered a hospital in her home town where a "spinal decompression" was performed, without relief of the spasms or their attending discomfort.

During the next six months the spasms increased so that she was forced to stop working. Walking became more difficult and she had to use a wheel chair or crutches. Six months before her present admission here she fell and fractured her left ankle. The fracture did not unite normally, the muscle spasms increased and after two months a bilateral cervical cordotomy was performed. Her discomfort was relieved but the spasms persisted and there was further loss of bladder control. Finally, she was transferred to this hospital with a tentative diagnosis of arachnoiditis for consideration of further surgery.

Physical examination revealed flexor and adductor spasms of both lower extremities. These were not abolished by the intravenous injection of 0.5 gm. sodium amytal. The patient was unable to stand alone and, when she attempted to walk with support, her gait was bizarre. Her legs jerked violently about in every direction, aimlessly and uncontrollably. Other noteworthy findings were those resulting from the previous operations: hypesthesia, loss of pain perception and loss of hot-cold discrimination up to C5 on the right side and C3 on the left. Knee jerks and ankle jerks were absent and the Babinski reflex was elicited bilaterally. There was complete anesthesia over the left foot and loss of proprioceptive sense even to gross movements of the toes and ankle of that side.

Blood count, urinalysis and blood chemistry were within normal limits. X-rays of the lumbar spine revealed only the sequelae of the previous laminectomies and fusions. Electromyograms of the muscles of the lower extremities revealed no evidence of spasm at rest or upon passive stretching. The record was interpreted as being "not remarkable," probably indicating "weakness of some of the tested muscles."

Because of her inability to walk even with crutches and the bizarre leg movements when attempting to walk with support, the puzzling muscle spasms, her open hostility to the doctors and the long story of operative procedures, it was decided to investigate the problem more fully from the psychiatric viewpoint. She was transferred to the psychiatric ward where our first effort was to secure a careful history of significant events in her life. She was the youngest of the family, having two older brothers. She had only vague memories of her mother who had been sick almost constantly. Her mother died when the patient was five, and she went next door to live with her grandparents who actually had been the main parental figures since her birth. They were elderly and strict. Her father contributed a small amount to the support of the patient and her siblings but was infrequently at home. He was an alcoholic who could be very pleasant when sober but he was rarely sober.

When the patient was eight, her older brother had poliomyelitis which left him with a weak right leg and a decided limp. This brother was the best friend and companion of her youth and she was sorely unhappy and disappointed when, at the age of fifteen, she was left alone by his departure to study for the priesthood.

In school her main interest was in dramatics and she had several leading parts in plays there. She did well but was unable to share her successes with her family who seemed unconcerned about this aspect of her life. Upon graduation from high school she won a scholarship to college; but when her father refused to advance her the additional funds needed, she was forced to give it up and go to work. One year later she had

saved enough to enable her to go to a small local college. There she did very well, was active in dramatics, was class president in her sophomore year and valedictorian of her class. Although at first she was frightened, she did begin having "dates" and enjoying the company of young men. Her escort for the sophomore prom, at which she was to lead the grand march, failed to appear the night of the dance. This was a bitter humiliation and she vowed that she would "manage" from then on and not get involved in situations in which she might be hurt by men. However, she was again hurt when, on the night of a play in which she starred, her father showed up very drunk, embarrassing her to tears.

Shortly after her graduation, her older brother was ordained a priest. At the party celebrating this, to the dismay of all, her father delivered a drunken oration on the evils of religion. Several weeks later she developed acute appendicitis and was operated upon. After this she became very "nervous," was unable to sleep and had marked anxiety symptoms, anorexia and weight loss. She had to give up her job and spent the next year at home. Over the space of a year the symptoms gradually disappeared. She then went on fairly well, working regularly and living with her grandparents who were quite old and feeble and required a considerable amount of attention.

Some three years after the onset of her back pain the grandmother died and eight months later the grandfather died. This left the patient alone as her father was seldom around. About two weeks after the death of her grandfather she developed acute lower abdominal pain and entered a local hospital where right ovariectomy and myomectomy were performed with relief of the pain.

After this she lived for a time in a boarding house with congenial friends and eventually took an apartment by herself. At the time she had her first and second operations here, her brother was also sick, having developed osteomyelitis of the right femur. During the next five years he had numerous operations on the thigh but finally was restored to health. At that time he returned to teach in a school in her city. She was overjoyed by this but found, to her sorrow, that they were no longer as close as in their youth.

Her father had died, meanwhile, and she said this was actually a relief for it removed the constant threat of his drunken behavior. She received none of his property and refused to contest the will saying: "He didn't want to give it to me when he was alive and I won't take it now."

Her social life, always active with friends in local theatrical groups, as well as her professional life, began to be constricted because of her increased difficulty in walking. About two years before the present hospitalization she found herself attracted to a divorced man whom she could not marry because of her religion.

In the interviews the patient told of an interesting series of experiences with doctors. When ten years old she was sent alone to the family doctor to be vaccinated. She did not know what to expect and when he told her to close her eyes, she thought she would get candy. Instead she got a series of sharp jabs with a needle. She opened her eyes in pain and astonishment and found that the doctor had collapsed, drunk, behind his desk. She was scolded when she told the story at home. In college she injured her wrist and the school doctor passed it off as merely a sprain. Twenty-four hours later she was unable to use the hand and x-rays showed a fracture. She said that because of these experiences she was loath to call a doctor when subsequently she developed abdominal pain and the appendicitis was far advanced at the time of operation.

The patient said that during the fourteen years of her back pain and its sequelae she had had great luck with her doctors. At home they were very kind and charged her nothing. She asserted that her feelings about the multiple unsuccessful operations were that occasionally doctors, even though highly skilled, fail, and that she just had a "run of bad luck."

When she came to the psychiatric ward, she was unable to walk and her legs were bruised from hitting the bars of the "walker." Her attitude was belligerent and skeptical as if to say: "Just try to help me and see where you get." Interviews were at first unproductive with only brief answers to direct questions and no elaboration by the patient. My own reaction to her hostile behavior was the immediate development of strong negative feelings toward her, which I was partly able to conceal from her. Within a week her attitude had changed. Originally she had said that she had no problems and nothing in her life was connected with her trouble. When I pointed out that it was of little value to her merely to answer questions, she understood and began to talk spontaneously. Concomitant with this her walking began to improve, actually before we had discussed any significant events or reactions in her life.

In regard to walking she expressed a feeling as though the lower part of her body were divorced from the upper, that she had no adequate image of her legs and no concept of where she should put her feet. She consciously mapped out the steps she took in relearning to walk. Her attitude to me changed markedly and she wanted to please me by making progress. After several weeks of interviews she told me that originally she had wanted to change doctors but decided against it as that would have been running away. She had been very upset because I had not showed my feelings and had said so little. She really had wanted me to indicate that I could see through her surface hostility and could understand that she really did not mean to act that way.

Early in the therapy my negative reaction to her changed to a positive one. We dwelt on linking her recent behavior to events in the past which had forced her to suppress emotions, behave coldly and test everyone she met.

As her walking continued to improve she asked permission to spend a weekend away from the hospital and this was granted. For the first time in two years she went out alone and had a very enjoyable time, caring for herself very well.

During the last week we discussed her relations with her brother and father and her reactions to them in terms of other men in her life. It seemed prudent not to delve deeply into this aspect of her life but we did bring out some of the factors in the relationship to her recent lover.

She spontaneously mentioned that when she first started walking it was to show the doctors they were wrong in thinking she was either lazy or emotionally upset. Later it was to please me, for I had become an important figure in her life. More recently, she has had a realistic desire to be able once again to assume an active place in society.

REPORT OF RORSCHACH TEST

MRS. DORIS GILBERT: The patient enjoyed taking the Rorschach test and, using the ink blots only as a minimal cue, produced highly imaginative and artistic stories in addition to the required responses. In general, the protocol suggests an integrated pattern of life, one that has functioned pretty well, perhaps not optimally. She has made use of sublimation, reaction formation, denial and has also found outlets in creative fantasy. Repression has operated fairly successfully, in that aggression is denied and relationships are presented as decidedly non-sexual. Relationships seem to be idealized—as though in terms of story-book roles—and she seems to "keep her distance" from people and from earthy, living reality.

The patient's female identifications are shadowy with a dominant theme of struggle or conflict over attaining a goal. Discouragement, with some tendency toward depression, is seen. It is interesting that many of her metaphors are in terms of *mobility*, suggesting that the leg symptom which immobilize her are a protection against the conflicts involved in striving for certain goals.

Many responses are strongly heterosexual in their symbolism with men depicted as givers of strength or vitality. However, she

cannot accept a dependent or submissive role because this, to her, means being trapped. Her tendency is to compete with men, to be like them, rather than accept the passive female role. She is desirous at all times of a certain amount of autonomy.

PRESENTATION OF PATIENT

The patient walked into the conference room on crutches. She was composed and friendly and expressed enthusiasm for her improvement. A brief neurologic examination by Dr. Cobb demonstrated the main features already reported.

DISCUSSION

DR. STANLEY COBB: It is surprising that she does not have more trouble with her sphincters. These bilateral cordotomies are rather risky. She is lucky to have such control with analgesia and hypalgesia up to C5 on the one side and C3 on the other. She has no position sense.

DR. WHITE: None at all in the legs.

DR. COBB: You would think she would have to walk ataxically but that does not show since she has relearned to walk. You would expect neurologically that she would not have spasm in view of the absent deep reflexes. This spasm was an un-neurologic symptom.

DR. HENRY H. BREWSTER: You felt hostile to her in the beginning? How did you change?

DR. WHITE: My interest increased. More material was coming out. It was obvious that this facade was covering an attitude of: "Please don't believe I am like this, because I am not. I need to have a good relationship with a doctor." Since then she has been able to form good relations with other physicians.

DR. EARL SOLOMON: I saw her on the neurosurgical ward and was pessimistic about transfer to our service. I am glad she was brought over now. I did not think psychotherapy would be effective.

DR. COBB: In summing up the Rorschach, was there evidence of hysterical conversion?

MRS. GILBERT: You could speculate about the meaning of the legs because of her emphasis on mobility and on striving toward goals.

DR. SAMUEL WALDFOGEL: The Rorschach is by no means typical of hysteria. One sees more maturity and much better personality integration than is customary in hysterical patients. Thus even though she responded to a severe crisis through the use of conversion symptoms, we may expect that her resources will make it possible for her to consolidate the gains she has shown in psychotherapy. She is capable of finding other solutions than regressive ones to her problems.

DR. COBB: The real story begins back at the age of twenty-eight, the immediate story of repeated operations. The earlier one —appendectomy—looked as if there had been adequate reasons. The mistakes began at the first laminectomy. The second one led to more trouble. Then the pain was relieved by the first cordotomy. Was there complete relief?

DR. WHITE: Complete relief for about three years.

DR. COBB: It is hard to go back and re-evaluate the mistakes in diagnosis and the amount of pain, etc. She did have repeated operations and the operations themselves left her much incapacitated. A permanent neurologic incapacity will remain. I do not suppose that she will improve much over what we see now. But that is an enormous improvement over what she had on arrival here. There is no neurologic explanation for the spasms. They were apparently a psychiatric manifestation. Dr. Lindemann, can you explain the mental mechanism?

DR. ERICH LINDEMANN: The circumstances surrounding the patient at the age of twenty-eight are not very clear. The symptoms, once the operations were done, were much colored by her relationship to a number of physicians. Doctors are important to her. There was at that time a definite disagreement between two neurologists and she was drawn into that. One said it must be a neurologic disorder; the other said, no. The one with whom she aligned herself said it was neurologic which meant that she

could not improve. When she came to us she was saying in effect that she could not re-align her loyalties. Her symptom was a failure to re-learn motor activity after the cordotomy. She had "disowned" that part of her body which neither she nor the doctor could understand. As she told Dr. White, it was a feeling as if the lower part of her body did not really belong to her. Her improvement here represents the resumption of control of her body. She is now eager to please us just as she was eager to please the neurologist who thought it was neurologic. Why she could do all this is a question. This is not typical hysteria with massive symptoms defended by the patient. She gives them up too readily. She is not frigid. She also should have had more symptoms in the "teen" age than she had.

She lost her mother at the age of five. The calamities started after her grandmother died which may have reactivated a state of perplexity. What one saw was a perplexity state in which she was unable to know with whom to align herself. She attempted to overcome that by assuming the type of role which Mrs. Gilbert inferred from the Rorschach; being the invalid in the wheelchair. This way, people could not be too close, could not question her adjustment. That waived the question of who she was. The degree of impairment of her motor functions depended upon the attitude of the doctor. She improved when we pushed her to exercise and to develop her capacity. I believe the problem was a lack of correct convalescence from a neurologic impairment with emotional strain rather than anything we could call "neurosis."

DR. COBB: Dr. White is to be complimented for handling this patient well and rather rapidly. We have seen a number of these people after cordotomy for pain. Some had repeated operations and in a number I have had the suspicion of a mechanism such as Dr. Lindemann outlined, but in none has it shown up so clearly as a problem of re-education which was inhibited by the wrong environment. There must be many patients who could have more function if they were handled this way, made to accept their legs and make the most use of them. I have seen polio patients after paralysis who were resistant to using muscles who, when treated psychiatrically, showed marked improvement.

DR. DANIEL DAWES: Is this case similar to what you see in children with learning difficulties? A child in school experiences a traumatic event. He reacts to it by refusing to learn. He tries to assert himself in that way. Is she not doing something of the sort? She experienced disturbances in her emotional life, refused to be aggressive and "lay down on the job." When she made a satisfactory relationship to the therapist she learned again.

DR. COBB: It is a learning problem, certainly.

DR. AVERY D. WEISMAN: If we had seen the patient before Dr. White worked with her, we might have called it a severe hysterical reaction.

DR. COBB: We do not really know what the original situation was. She had a myelogram and then operation and there is no evidence in the record whether a disc protrusion was doing harm or not.

COMMENT

This case illustrates how the psychodynamic understanding of a puzzling illness may clarify the diagnosis, suggest appropriate treatment and enable one to reach a fairly dependable prognostic opinion. The patient had a long history of pain, multiple operations on the spine and spinal cord, peculiar muscle spasms and inability to control the movements of her legs. The pseudoneurologic symptoms and the patient's hostile attitude impressed the initial examiners as indicative of a severe psychoneurotic illness. Hysteria with conversion symptoms and "surgical addiction" was the tentative diagnosis and the outlook for anything less than chronic invalidism was not hopeful.

In psychiatric interviews, however, the patient dropped her facade of hostility and talked freely about her experiences, problems and conflicts. It became apparent that

the dynamic structure of her illness was not characteristic of hysteria but seemed rather a problem in re-learning motor control. Her positive relationship and loyalty to her former doctor (who had maintained that the symptoms were neurologic) had been a very important factor; when she transferred her confidence and faith to another doctor, one who *expected* her to assume control of her legs again, a significant part of the therapeutic process was accomplished. The inability to use her legs was employed unconsciously by the patient as a means of solving a conflict, as was suggested in the Rorschach responses and as briefly formulated in the discussion by Dr. Lindemann.

Treatment was brief and no special efforts were made to study the patient's character structure or to elucidate the origin and meaning of the symptoms. The therapeutic goal was limited; the focus being upon mobilization of the patient, helping her to resume motor control of her legs within the limits of her physical resources.

Further information is lacking concerning the original complaint. It was never definitely established that the protruding intervertebral disc actually caused compression of the spinal nerve roots. One is tempted to speculate as to the significance of the fact that her older brother (who had been so important to her in childhood) had a weak right leg. The patient's first sciatic symptoms were on the right side. Another interesting coincidence was the fact that the brother was sick with osteomyelitis of the right femur at the time of the patient's first and second laminectomies.

One cannot reconstruct a satisfactory formulation of the early stages of the patient's illness because the data are lacking, but certainly one factor of great importance stands out, namely, the disagreement among the various consultants as to the basis of the symptoms. It is a misconception (unfortunately still deeply ingrained in medical thinking) to regard symptoms as *either* "functional" *or* "organic" rather than thinking of them in terms of *how much* they are related to structural changes and *how much* due to emotional conflicts. In this case there was permanent neurologic disability due to the operative procedures but the attitude of the patient and her reactions to internal conflicts and external stresses could make the difference between a life of invalidism or one of activity and independence. We do not know how many patients with neurologic lesions (due to injuries, operations, poliomyelitis, etc.) are unduly crippled by their illness, but the number must be considerable. In many such cases the dynamically oriented psychiatrist can help materially in the rehabilitation of the patient.

Follow-up Note. Six weeks after discharge she has continued to improve. Her walking is steadier, she has been actively taking care of her apartment and has been busy with plans for working. Her social contacts are being resumed and she looks forward confidently to further improvement.

Clinico-pathologic Conference

Exsanguinating Hemoptysis

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. S. (No. 139152), was a sixty-three year old white married farmer who entered the Barnes Hospital for the first time on September 7, 1946, complaining of "bleeding from the lungs." The family history was of interest in that his half sister had had known tuberculosis and his brother had died of pulmonary hemorrhage. Nothing was known of the patient's contact with his brother, but he had had only slight contact with the tuberculous sister. The patient himself had enjoyed good general health. He had pneumonia at the age of eighteen and again at thirty-six, and when he was fifty he was bothered with "sciatica." He was able to do his farm work without difficulty prior to the present illness.

About four to five years before admission the patient noted increasing fatigue which caused him to limit his working hours to five or six daily. Concomitantly there was a decrease in appetite and slight weight loss. Six months before admission he had an illness described as "the flu"; subsequently, he was bothered by a persistent non-productive cough. Several months later he developed a slight "sticking pain" in the lower right chest which lasted only a few minutes; although it recurred, it was never pleuritic in character. Twelve days prior to entry he suddenly coughed up about a cupful of dark red blood. At the time there were no other symptoms. In the twelve days which elapsed before admission he had produced occasional blood-streaked sputum. He consulted a physician who advised a chest x-ray; the patient was told that he had a "spot in the right lung." On the day of admission while driving his wagon he suddenly coughed up dark blood once again and soon thereafter had a massive pulmonary hemorrhage. He became unconscious and was taken to his physician's office; there he regained consciousness while receiving parenteral fluids and was sent to the Barnes Hospital.

Physical examination revealed his temperature to be 37.6°C., pulse 84, respirations 42 and blood pressure 124/85. The patient did not appear ill and exhibited no respiratory difficulty. He was slightly pallid. There was no generalized lymphadenopathy. Examination of the eyes revealed no abnormalities. The upper respiratory tract likewise appeared normal. On examination of the chest there was dullness to percussion at the right base and transient coarse rales were heard adjacent to the spine in this area, but no other pulmonary abnormalities were noted. The heart was normal as was the abdomen. The fingers were not clubbed.

The laboratory data were as follows: *Blood count:* red cells, 4,220,000; hemoglobin, 14 gm.; white cells, 8,100; differential count: within normal limits. *Urinalysis:* negative. *Blood Kahn test:* negative. *Blood chemistry:* non-protein nitrogen, 29 mg. per cent; total protein, 6.4 gm. per cent; albumin, 3.9 gm. per cent; globulin, 2.5 gm. per cent. *Roentgenogram of the chest:* The cardiovascular silhouette was within normal limits except for a slightly prominent aortic bulb. Calcification was seen in both hilar regions and in the periphery of the left lung. There was slight apical scarring. The bronchial markings were quite coarse and feathered along the descending bronchi on

the right and to a lesser extent on the left; a small amount of pneumonitis was present and, in addition, there was some pulmonary infiltration in the fourth and fifth right anterior interspaces extending out to the periphery. Its exact nature was not evident and it was thought perhaps to represent blood in the alveoli. *Electrocardiogram:* within normal limits.

The patient was placed on respiratory isolation and sedated. He received 40,000 units of penicillin every three hours. Several sputum specimens were negative for acid fast organisms and guinea pig inoculations were negative. The patient was referred to the Surgical Chest Service for consultation. There a diagnosis of minimal bronchiectasis of the right lower lobe was made. The patient was not subjected to bronchoscopy. The pneumonitis present on entry gradually cleared and blood disappeared from the sputum. Stool specimens, however, were consistently guaiac positive. At no time did the patient exhibit anemia. A blood culture drawn on entry was negative and sputum cultures were negative for fungi. During his hospital stay the patient's temperature ranged between 37° and 37.5°C. He left the hospital on September 20, 1946, apparently well.

Following discharge from the hospital the patient continued to have a mild cough, particularly in the mornings; at that time he would produce small amounts of mucopurulent sputum. He felt quite well and was able to work. Two years before the second admission a follow-up chest film was negative. Two and a half months prior to entry the patient suddenly coughed up about a teaspoonful of bright blood. Several weeks later he again coughed up two to three cupfuls of dark blood following an attack of repeated sneezing. He became dizzy and weak and was bed-ridden for six days. One day prior to entry he came to the Washington University Clinic where a few moderately coarse rales were heard at the base of the right lung. A film of the chest revealed findings considered to represent a shrunken middle lobe and there was increased density at the right hilar region. A tentative diagnosis of bronchogenic carcinoma was made and the patient was advised to enter the hospital. On the following morning, October 17, 1950, the patient suddenly coughed up a large amount of blood and was brought to the Emergency Room of the Barnes Hospital. While being examined he produced two and one-half emesis basins of blood and was immediately admitted.

Physical examination at the time of entry revealed the temperature to be 37.2°C., pulse 120, respirations 30 and blood pressure 140/70. The patient was acutely ill and apprehensive but was not pale. The only changes from the previous examination were the presence of arteriolar narrowing in the fundi and dullness at the right base. Careful auscultation of the lungs was impossible because of rales and rattles therein.

The laboratory findings were as follows: *Blood count:* red cells, 4,370,000; hemoglobin, 13 gm.; white cells, 4,050; differential count: basophiles 1 per cent, eosinophils 1 per cent, stab forms 2 per cent, segmented forms 52 per cent, lymphocytes 41 per cent, monocytes 3 per cent; hematocrit 37 per cent; platelets adequate. *Urinalysis:* negative. *Blood chemistry:* non-protein nitrogen, 20 mg. per cent; fasting blood sugar, 86 mg. per cent; total protein, 6.1 gm. per cent; albumin, 4.3 gm. per cent; globulin, 1.8 gm. per cent. *Sputum smears:* no acid fast bacilli. *Sputum culture:* negative for pathogenic organisms.

The patient was maintained on complete bed rest and was given 100 mg. of demerol, and penicillin and streptomycin. Active bleeding stopped although the patient continued to cough up small amounts of bright blood. On the day following admission the hematocrit was 32 per cent. On the third hospital day the patient's blood pressure suddenly fell to 80/50. The pulse rate, however, was not elevated. After intravenous saline infusion the blood pressure rose to 110/70, only to fall again to 85/50. He was given a transfusion and subsequently the blood pressure ranged between 110/70 and 90/50. Oxygen therapy, which had

been instituted shortly after admission, was discontinued because the patient appeared to be resting comfortably. Dullness continued to be noted at the right base where breath sounds were absent. Although rales persisted on the right, the other adventitious sounds decreased. Cytologic examination of the sputum was negative for carcinoma cells. On October 20, 1950, the fourth hospital day, the patient suddenly developed massive hemorrhage and blood gushed from his nose and mouth. Bleeding continued despite all emergency measures and the patient died.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: The diagnostic problem in this case is made more difficult by the fact that the patient had a pulmonary hemorrhage four years prior to his final episode and was then quite well in the intervening period. Certainly in a patient of this age pulmonary hemorrhage brings to mind bronchogenic carcinoma, but it would seem unlikely that carcinoma should have caused bleeding four years previously and then remained asymptomatic until the terminal episode. The diagnosis of carcinoma, however, was suggested at the time the patient was seen in the Clinic the day before he came into the hospital. Dr. Fee, would you tell us on what basis the x-ray department made a diagnosis of carcinoma?

DR. WESLEY FEE: We took into consideration the fact that the patient had a mass in the right perihilar region, plus the signs of collapse of the right middle lobe. These x-ray findings, in combination with the history of hemoptysis, make carcinoma the most likely possibility. Needless to say we were unable to make an unequivocal diagnosis; we merely indicated that in our opinion carcinoma was the most likely explanation for the x-ray findings.

DR. ALEXANDER: Would you care to make any comment on the films taken at the time of the first admission?

DR. FEE: In the earlier films the heart and aorta were normal. A rather homogeneous density was seen in the lower portion of the right lung field; in view of the hemoptysis a few days earlier it was thought that the density might represent blood in the alveoli. Bronchograms were performed at the time and were interpreted by us as being within normal limits but, in retrospect, slight irregularity in the right middle lobe bronchi certainly should have suggested to us, as it did to the chest surgeons, the possibility of bronchiectasis. Even with these films, however, the diagnosis could not have been made with assurance.

DR. ALEXANDER: Considering the final massive hemoptysis, would you in retrospect be willing to make a diagnosis of carcinoma on the basis of the earlier films?

DR. FEE: No, I do not think so.

DR. ALEXANDER: Thank you, Dr. Fee. We take it then that the x-ray department made a diagnosis of bronchogenic carcinoma on a statistical basis but did not consider it the only possibility by any means.

DR. FEE: That is right.

DR. ALEXANDER: The diagnosis of minimal bronchiectasis was made by the chest surgical service when the patient was here four years ago. Dr. Peters did not see the patient, but I have asked him if he would comment on that diagnosis, based on the patient's findings at that time.

DR. RICHARD M. PETERS: Unexplained hemorrhage plus incomplete filling of the bronchi of the middle lobe probably suggested bronchiectasis to those who saw the patient in 1946. As has been noted by Dr. Fee, it would not have been possible to make an unequivocal diagnosis of bronchiectasis at that time, since failure of the bronchi to fill with lipiodol may be due to a technical difficulty rather than to anatomic change. The fact that the lymph nodes in the hilum were calcified suggests to me one other possible cause of hemorrhage, namely, erosion of a bronchial artery by a calcified hilar lymph node.

DR. ALEXANDER: May massive hemorrhage result from minimal bronchiectasis?

DR. PETERS: I have seen severe hemorrhage occur in patients with minimal

bronchiectasis which involved only one lobe and which was considered too minimal to indicate resection. Hemorrhage is particularly apt to occur at a time when there is an associated acute respiratory infection. In such patients bronchograms may show bronchiectatic changes in only a single bronchus.

DR. ALEXANDER: That is a very important point. If we assume that bronchiectasis was the primary lesion in this man, is it conceivable that massive hemorrhage leading to his death could have resulted from relatively minimal bronchiectasis?

DR. PETERS: In general it is said that patients do not bleed to death from bronchiectasis. I believe that that is also your opinion, is it not, Dr. Goldman?

DR. ALFRED GOLDMAN: I have never seen a fatal hemorrhage in a patient with bronchiectasis, but in his book Dr. Graham mentions that it does occur rarely.

DR. PETERS: I discussed this question with Dr. Burford who also believes that it is rare for patients to exsanguinate as a result of bronchiectasis. He has himself not actually seen death from hemorrhage in bronchiectasis, but has seen several patients in whom the bleeding was so massive that emergency resection was performed. I doubt that anyone would have considered emergency resection in this patient. In the first place, until the terminal episode there was no reason to suspect that he would bleed so massively. Furthermore, he was a rather elderly man who probably had some emphysema. As a matter of fact, when he was seen on the chest service in 1946, a note was made that he did have significant emphysema and resection probably would have left him a severe respiratory cripple. Most patients with such minimal disease will do well without surgery.

DR. ALEXANDER: The patient did have a slight productive cough during the interval between his first and second admissions. Would that be compatible with bronchiectasis, Dr. Goldman?

DR. GOLDMAN: Yes.

DR. ALEXANDER: If this patient had bronchogenic carcinoma, did it arise in the bronchiectatic area? How often does bronchogenic carcinoma occur in association with bronchiectasis?

DR. PETERS: Usually carcinoma of the bronchus, particularly if it is in the main bronchus, is manifested by the symptoms of obstruction and peripheral infection. Thus when resection is performed for a tumor of one of the major bronchi, bronchiectasis is almost always found distal to the lesion. Probably the tumor is the horse and not the cart. On the other hand, frequently it is not possible to say that the patient did not have bronchiectasis prior to the development of carcinoma. I would like to point out that it is extremely rare, except in terminal bronchogenic carcinoma, to have massive hemorrhage of the order which occurred here. Patients with bronchogenic carcinoma often have bloody sputum, but bleeding is usually not massive unless the tumor is far advanced. In such a case I would have expected a larger mass to have been demonstrated by x-ray than was seen here.

DR. ALEXANDER: Dr. Goldman, do you agree that carcinoma and bronchiectasis probably bear no particular relation, one to the other, except as Dr. Peters has indicated?

DR. GOLDMAN: Yes, I would think that in most instances in which bronchiectasis is found distal to a carcinoma, it is reasonable to assume that it arose incidental to the carcinoma.

DR. ALEXANDER: Pursuing this particular thought further, I should like to ask Dr. Moore whether the changes in the epithelial lining of the bronchus which occur in bronchiectasis would make bronchogenic carcinoma more apt to develop.

DR. ROBERT A. MOORE: I think that is possible, Dr. Alexander, although I also agree completely with Dr. Peters that all the evidence points to the fact that bronchiectasis when seen with carcinoma is secondary to it. It is rare for one to be able to establish, with any reasonable degree of certainty, that carcinoma has originated in an ectatic bronchus.

DR. ALEXANDER: If we discard the diagnosis of bronchiectasis and carcinoma, the next question to be answered is whether the x-ray findings, particularly on the last admission, are compatible with bronchiectasis alone. Dr. Goldman, do you believe that this patient had bronchiectasis as a primary disease?

DR. GOLDMAN: The original film, as has been pointed out, certainly showed very little bronchiectasis. One would, therefore, have to doubt that the primary diagnosis was bronchiectasis. The films taken at the time of the last admission, however, showed atelectasis of the right middle lobe, a finding compatible with bronchiectasis. One can only say that there was atelectasis, and he cannot define the nature of the lesion producing atelectasis.

To return to the question of fatal hemorrhage in bronchiectasis, as I indicated, I have never seen it. I have seen one patient in whom I believe death would have occurred had it not been for the induction of an artificial pneumothorax. It is of interest that patients with bronchiectasis who bleed the most severely are those who produce the least sputum.

DR. PETERS: Should we not re-emphasize, Dr. Goldman, that bleeding usually occurs concomitantly with respiratory infections?

DR. GOLDMAN: Yes, I would agree with that. Of course, severe bleeding may occur in the absence of bronchiectasis, carcinoma or tuberculosis. In Jackson's series of pulmonary hemorrhage in non-tuberculous patients, the third most common cause was severe acute tracheobronchitis.

DR. HENRY A. SCHROEDER: It should be pointed out, Dr. Alexander, that since this patient was emphysematous, his pulmonary arterial pressure was probably elevated. In such an instance hemorrhage might well have been more severe than it would have been in a person with normal pulmonary artery pressure; the latter tends to be low.

DR. W. BARRY WOOD, JR.: As I understand it, in bronchiectasis the site of bleeding is the bronchial artery. Emphysema, which changes the pulmonary artery pressure, does not influence the systemic pressure and, therefore, in bronchiectasis emphysema should not be a factor in increasing bleeding. In tuberculosis, on the other hand, when cavities erode a vessel, the pulmonary artery or one of its branches may be involved; in that situation bleeding might be accentuated by the presence of emphysema.

DR. ALEXANDER: Your comments are well taken, Dr. Wood. Earlier in the discussion it was mentioned that bleeding may have arisen as the result of erosion of a bronchial artery by one of the calcified hilar lymph nodes. Dr. Flance, does massive hemorrhage occur under such circumstances?

DR. I. JEROME FLANCE: Severe hemorrhage from erosion of a bronchial artery by a calcified node certainly is seen. Usually the hemorrhage does not assume massive proportions, however; I have never seen a fatal one.

DR. MOORE: I have seen an autopsy on one patient who had a fatal hemorrhage as a result of erosion of the pulmonary artery by a very anthracotic lymph node. I believe this chain of events arise much more often with anthracosis than with tuberculosis.

DR. PETERS: It is of interest to point out in that regard that when atelectatic lobes are resected because of obstruction by broncholiths, the broncholiths are often left in place because they are adherent to the bronchial artery and it is too hazardous to attempt to remove them.

DR. THOMAS H. HUNTER: Should we not consider here the possibility of hereditary telangiectasia which may occur in this age group without having ever manifested itself before? Lesions in hereditary telangiectasia may involve the bronchi as well as occur as pulmonary arteriovenous fistulas. Two points suggest this diagnosis to me. First, the patient's brother died of pulmonary hemorrhage of unknown origin. Second, the patient had unexplained blood in his stool at a time when he was not bleeding from the lung. Telangiectasia may, of course, also involve the gastrointestinal tract, and much of the history and findings are compatible with that diagnosis.

DR. ALEXANDER: That is a very good suggestion, Dr. Hunter.

DR. SAMUEL C. BUKANTZ: Does the color of the blood in massive hemoptysis help in localizing its origin?

DR. PETERS: Probably not.

DR. ALEXANDER: We now have as possibilities bronchiectasis, erosion of a bronchial artery by a calcified hilar node and hereditary telangiectasia. Are there any other diagnoses which should be considered?

DR. ROBERT J. GLASER: I do not think that carcinoma can be dismissed as a possibility.

DR. ALEXANDER: I would agree with you; we shall include it in our list.

DR. CARL G. HARFORD: The severe hemorrhage four years ago with an uneventful interim mitigates against carcinoma in my opinion, but perhaps some other malignant but more slowly growing tumor, such as lymphoma, should be mentioned.

DR. ALEXANDER: What about bronchial adenoma, Dr. Peters? Does it grow slowly?

DR. PETERS: Yes.

DR. ALEXANDER: May it be carcinomatous?

DR. R. A. MOORE: They should certainly be treated as a malignant tumor.

DR. ALEXANDER: We should also consider tuberculosis. The patient had a sister who died of tuberculosis, and the fact that his brother had pulmonary hemorrhage would suggest the same diagnosis. Further, the patient lost weight, his appetite was poor and he had calcification in the lung. Are there any other questions or comments?

DR. FLANCE: This situation is so unusual that it suggests to me a rather rare lesion. One in particular which should be mentioned, I believe, is an aneurysm of the bronchial artery. The dramatic fashion in which death came to this man suggests an erosion of a major vessel and, aside from carcinoma, none of the diagnoses mentioned seems very likely to me. I would agree that carcinoma would be ruled out on the basis of a hemorrhage four years previously with no bleeding in the intervening years. I do not think the patient had tuberculosis.

DR. ALEXANDER: Are the x-ray findings compatible with bronchial artery aneurysm?

DR. FLANCE: I do not think there are any specific x-ray signs of bronchial artery aneurysm. Atelectasis such as was seen here might occur as a result of bronchial compression.

DR. ALEXANDER: It seems to me that the critical point in this case is the fact that the patient died of massive hemorrhage; thus whatever diagnosis we choose must be compatible with such a terminal episode. Dr. Goldman, on the basis of your experience, would you list the diagnosis which you believe most likely to be correct.

DR. GOLDMAN: Putting them all together, I would consider bronchiectasis first.

DR. ALEXANDER: Dr. Wood, what is your choice?

DR. WOOD: I am impressed by the x-ray findings and particularly by the calcification in the lymph nodes. I believe that erosion of a bronchial artery by a calcified lymph node was responsible for the hemorrhage and would list tuberculosis of the node as the underlying lesion.

DR. ALEXANDER: How would you explain the atelectasis?

DR. WOOD: By pressure of the node on the bronchus. What is your opinion, Dr. Alexander?

DR. ALEXANDER: I believe that the patient had bronchiectasis.

DR. PETERS: Dr. Wood, if you make a diagnosis of tuberculosis, do you not think it should be pointed out that the patient had healed tuberculosis? You do not think this man had active tuberculosis, do you?

DR. WOOD: No, I would agree with you.

DR. ALEXANDER: In summary, I think that we can do little but list the possibilities which were suggested. Perhaps bronchiectasis has received more support than the other possibilities, but tuberculosis of the hilar lymph nodes with calcification and erosion of a bronchial artery, hereditary telangiectasia, bronchial artery aneurysm, carcinoma and lymphoma have also been suggested.

Clinical Diagnoses: ? Bronchiectasis; ? tuberculosis of the lymph nodes, inactive, with erosion of a bronchial artery; ? carcinoma of the bronchus; ? bronchial artery aneurysm; ? hereditary telangiectasis; ? lymphoma.

PATHOLOGIC DISCUSSION

DR. JAMES C. ROBERTS: No abnormal fluid was noted in any of the serous cavities. The lungs weighed 1,830 gm. and were black and congested. The trachea and major bronchi, especially those of the right middle and lower lobes, were filled with bloody mucus and fluid. The middle lobe of the right lung was firm and contracted toward the hilum with dense adhesions to the inferior surface of the upper lobe. Particularly in the lower lobes there were dark red, firm, pyramidal foci that extended to the pleura and had the appearance of recent hemorrhage into the pulmonary alveoli. The hilar lymph nodes were enlarged, black, firm and fibrous. At the hilum of the middle lobe of the right lung a group of these firm nodes compressed the main bronchus; beyond that point the bronchus was dilated and surrounded by the fibrotic, atrophic pulmonary parenchyma. The bronchus of the lower lobe of the right lung was minimally dilated. Black pigment, similar to that in the lymph nodes, was present in the walls of pulmonary arteries and beneath the mucosa of bronchi adjacent to fibrotic nodes in several sites. No definite rupture of a blood vessel or other obvious sources of bleeding was discovered despite careful dissection of all the bronchi and arteries. Incidental lesions in the lungs included calcified and fibrous scars of the type resulting from first-infection and re-infection tuberculosis, but there was no evidence of active tuberculosis.

About 1,000 cc. of blood-tinged fluid were present in the mouth, pharynx, esophagus and stomach but no source of the bleeding was identified in these sites. The heart was dilated, particularly its right chambers but only slightly hypertrophied. In the abdominal viscera there was slight congestion of the liver and spleen and an adenomatous polyp 8 mm. long in the sigmoid colon. The surfaces of the polyp were not eroded and there was no evidence of old bleeding at that site.

FIG. 1. Small bronchi at the hilum of the middle lobe of the right lung. There is atrophy and fibrosis of the walls of the bronchi, interstitial fibrosis in the lung, cuboidal epithelium lining some alveoli and recent hemorrhage interstitially and in the lumens of the bronchi. The stenotic segment of the main bronchus was similarly involved.

DR. GUSTAVE J. DAMMIN: Grossly the diagnosis of anthracosilicosis was indicated by the strikingly enlarged and firm hilar lymph nodes. Obvious stenosis of the bronchus to the middle lobe of the right lung and the associated bronchiectasis, fibrosis and atrophy in that lobe were the major evidences of chronic disease that seemed to be related to this patient's history. The relationship of the large amount of hemorrhage in the lungs to the death of the patient was obvious, but the origin of that hemorrhage was not grossly apparent. There was, however, one important bit of evidence concerning the source of the hemorrhage. The middle lobe of the right lung was fibrotic and contracted. It had obviously not been functioning for some time, yet its bronchi were filled with blood and there was hemorrhage in the parenchyma. It seems apparent such hemorrhage had to originate in that lobe and could not have been aspirated into it as was the blood in the functioning lobes.

Histologic investigation gave further evidence that there was an active disease in the right middle lobe to account for the hemor-

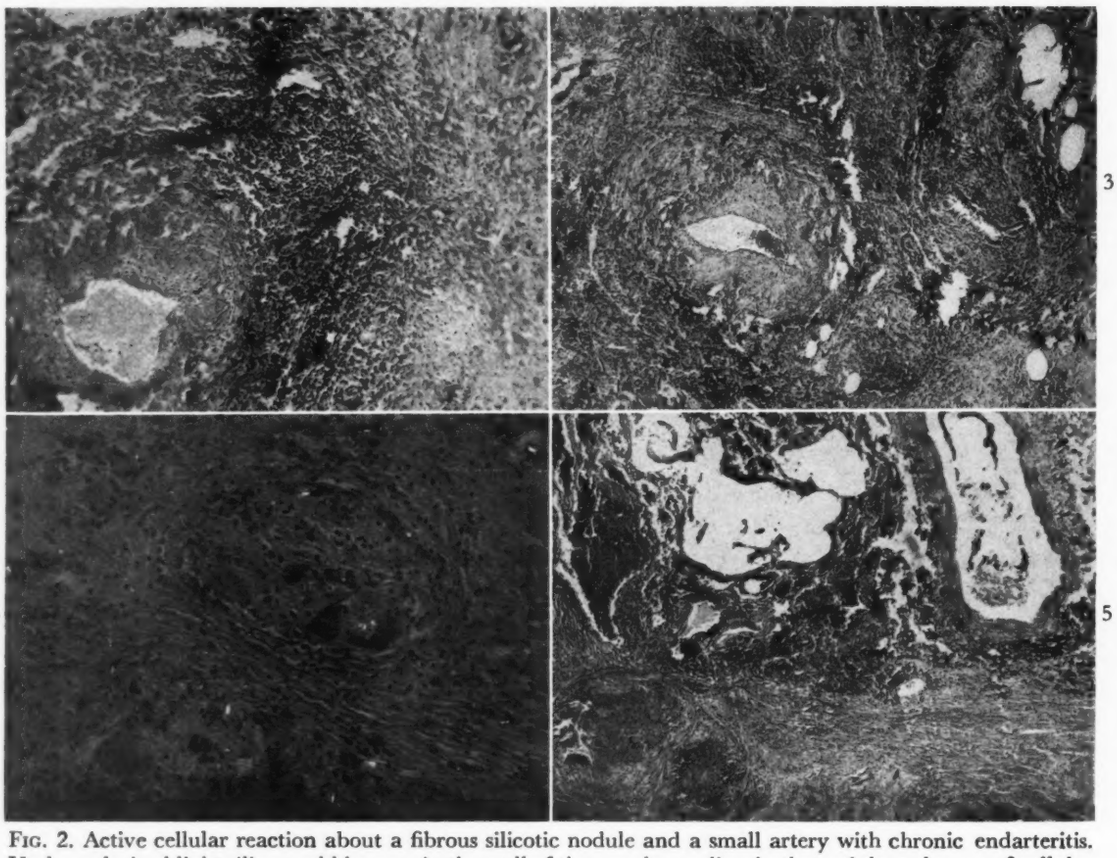


FIG. 2. Active cellular reaction about a fibrous silicotic nodule and a small artery with chronic endarteritis. Under polarized light silica could be seen in the wall of the vessel as well as in the nodule and area of cellular infiltration.

FIG. 3. Interstitial fibrosis and hemorrhage in the middle lobe of the right lung. The location of the blood and the fibrotic nature of this lobe indicate that the hemorrhage arose in this structure.

FIG. 4. A collection of giant cells containing doubly refractile crystals, presumably silica, in one of the foci of active cellular reaction in the lungs; photomicrograph taken with polarized light.

FIG. 5. Aspirated blood in the alveoli of the lower lobe of the right lung over a pleural scar. There is no evidence of interstitial hemorrhage like that in the middle lobe.

rhage. The section in Figure 1 was taken near the point of origin of the bronchus to that lobe. In it there are three small bronchi filled with hemorrhage. The walls of these bronchi show atrophy of their usual components and increased amounts of fibrous tissue. There is hemorrhage in the interstitial tissue and at the edge of this illustration there are a few alveoli lined by high cuboidal epithelium, two findings that were constantly present in all sections from this lobe. Figure 2 illustrates a region near a large silicotic nodule, the coarse collagenous fibers of which are on the right side of the photograph. At the periphery of that nodule there is an artery with distinct fibrous thickening of the intima and heavy round cell infiltration with some giant cells about the adventitia. Under polarized light there are small, sharp, doubly refractile crystals throughout the section, especially about and within the wall of this vessel. The cellularity of this and other lesions in the middle lobe of the right lung indicates an active reaction, presumably progressive silicosis. There are no true tubercles with caseous necrosis to suggest that the tubercle bacillus was responsible for any part of these lesions.

In Figure 3 there is another bronchus and vessel surrounded by fibrotic interstitial tissue. The hemorrhage in this interstitial tissue is repeated evidence that the bleeding arose in that lobe. Under polarized light doubly refractile particles were seen throughout this section as well as in sections

from other lobes. Some of these particles enclosed in multinucleated giant cells are illustrated in Figure 4. Finally, Figure 5 illustrates one of the foci of hemorrhage in the other lobes. Here the blood is confined to the lumens of the alveoli; and although there is a dense subpleural scar in the lower part of the photograph, there is no evidence of interstitial hemorrhage.

The pathologic lesions in this case center about anthracosilicosis that was both chronic and active. The degree of fibrosis in the lung and lymph nodes was compatible with a duration of four years as indicated by the history. The involvement of lymph nodes at the hilum of the middle lobe of the right lung led to pressure upon and spread of the fibrotic reaction into the wall of the bronchus with consequent stenosis, bronchiectasis, atrophy, atelectasis and fibrosis. This was an example of what Graham and others* have called "middle lobe syndrome." They quote evidence that the middle lobe bronchus is especially susceptible to involvement by processes in the surrounding lymph nodes with subsequent stenosis and atelectasis of that lobe. In seven of their twelve cases, none of which were due to tuberculosis, hemoptysis was the presenting symptom. The best apparent explanation for the terminal hemorrhage in this case was that it arose interstitially in the middle lobe of the right lung as a result of the continued activity of the anthracosilicotic process.

There was no evidence that chronic infection was responsible for any more of the fibrosis and contraction of the right middle lobe than is ordinarily seen after obstruction of a bronchus. It could be postulated that this patient had several recurrent bouts of pneumonitis which caused the enlarged nodes, possibly adding to the effects of silicosis; with resulting fibrosis the changes in the right middle lobe could have been produced. It seems more likely, however, from the microscopic observations and from what is known about the disease, that silicosis was responsible for the process which was gradually progressive over this long period. Although there were typical lesions to indicate this patient had tuberculosis at least twice in his life, there was no evidence it was active at the time of his death or that it was responsible for the lesions associated with his illness.

Dr. Wood: There were two misleading features in this case. First, the patient's occupation was stated to have been a farmer; second, our interpretation of the densities thought to be calcium in the roentgenograms. It is unlikely that a person would have sufficient contact with silicious dusts while working on a farm to cause clinical disease. A more complete occupational history might have mentioned employment in a coal mine or quarry and have suggested the proper etiology in this case. In taking a clinical history it is not enough to ask a person what his occupation is at that time; it is a question of what he has done all his life. In regard to the calcification, does uncomplicated anthracosilicosis proceed to calcification?

Dr. Dammin: Calcification has been observed in experimental silicosis and rarely in what were thought to be uncomplicated human cases; as a rule, however, calcification in association with silicosis is due to some complicating factor such as coexistent tuberculosis. In this case, the only calcified lesions observed at autopsy were those of a primary complex in the left lung on the side opposite to the lesion we interpret as principally related to the patient's symptoms.

Final Anatomic Diagnoses: Anthracosilicosis of the lungs and the hilar, mediastinal, and subdiaphragmatic lymph nodes; stenosis of the bronchus to the middle lobe of the right lung; bronchiectasis of the middle lobe of the right lung with atrophy and fibrosis of the pulmonary parenchyma; interstitial hemorrhage in the middle lobe of the right lung; aspirated blood in all lobes of the lungs.

Acknowledgment: The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

* Graham, E. A., Burford, T. H. and Mayer, J. H. Middle lobe syndrome. *Postgrad. Med.*, 4: 29–34, 1948.

Case Report

Subacute Bacterial Endocarditis Successfully Treated with Aureomycin*

SIDNEY O. HUGHES, M.D.
Philadelphia, Pennsylvania

AUREOMYCIN has proved effective in a wide variety of infecting agents. Besides many bacteria aureomycin has proved useful against protozoa and spirochetes, rickettsia, virus and viral-like agents such as pleuropneumonia organisms. An extensive review of the literature reveals a few reports of the use of aureomycin in subacute bacterial endocarditis with varied results. Long[1] cites two cases of patients with subacute bacterial endocarditis caused by Streptococcus faecalis who were treated successfully and followed for four months while Brainerd[2] treated two similar patients with only a temporary clinical response. Harvey[3] reporting four cases obtained a favorable result in only one. Dowling[4] collected two cases, and one of the patients recovered. Astler[5] reported two cases, one due to Str. faecalis, treated with a combination of aureomycin and chloramphenicol with a clinical response, but the blood culture remained positive. The other case succumbed from embolic complications. Allen[6] reports a case of a patient who died from ulceration through the septum. A recent case discussed in a clinico-pathologic conference[7] responded clinically but the patient died of renal failure.

It is the purpose of this article to report three cases successfully treated with aureomycin and followed for periods of seven, ten and four months.

CASE REPORTS

CASE 1. The first and most striking case is that of a thirteen year old Italian girl who was first admitted to the Presbyterian Hospital on November 9, 1948, with fever and joint pains. Past medical history included tonsillectomy at the age of four, rheumatic fever with chorea at the age of five which persisted for a year and pneumonia at the age of nine. From nine to thirteen she had occasional bouts of fever and joint pain. She had had one chill in the summer of 1947 and had lost weight.

On admission she appeared undernourished, was febrile and had an enlarged liver palpable 2 cm. below the costal margin. A grade II systolic murmur was heard at the third interspace to the left of the sternum. A soft, blowing, aortic diastolic murmur was heard transmitted to the same area. The left ankle was slightly swollen and tender. No petechiae were noted. Laboratory data revealed a hemoglobin of 8.5 gm., 58.2 per cent, red cell count 4.35 million, leukocyte count 10.25 thousand, with a normal ratio of cells. The sedimentation rate (Westergren) was 48 to 118 mm. in one hour. The urine gave a 2 plus reaction for albumin. Eleven blood cultures were sterile. Electrocardiograms were repeatedly essentially normal.

The course was that of a long febrile illness with temperature varying between 99°F. and 101°F. and occasionally rising to 102°F. On the fifteenth hospital day the spleen was palpable and on the forty-fifth and sixtieth days ecchymoses were noted on the plantar surface of the right first toe and right elbow, respectively. The murmurs varied from day to day and frequently the diastolic component could not be heard. On the forty-fifth day penicillin and carinamide were prescribed in doses of 1 million units a day and 15 gm. a day, respectively, for forty days. The temperature gradually came down to normal, the sedimentation rate dropped

* From the Medical Division, Presbyterian Hospital, Philadelphia, Pa.

to 42 mm. in one hour and the diastolic murmur disappeared completely. She was discharged on the hundredth day.

She was followed regularly in the outpatient department, was afebrile and gained weight until October, 1949, when further elevation of the sedimentation rate developed to 91 mm. in one hour and the basal diastolic murmur recurred. She was readmitted on October 13, 1949, to Presbyterian Hospital.

On the second admission physical examination disclosed a normal temperature, slight tachycardia and the same murmurs that were presented on the first admission. The spleen and liver were not palpable and no petechiae were noted. Laboratory studies revealed a hemoglobin of 12.6 gm., 86 per cent, red cell count 3.9 million, leukocyte count 5.3 thousand with 61 per cent filamented neutrophils, 7 per cent non-filamented neutrophils, 1 per cent eosinophils and 29 per cent lymphocytes. Sedimentation rate was 77 mm. in one hour. The urine gave a 2 plus reaction for albumin.

On the twelfth hospital day the patient had a chill and the temperature rose to 103°F. A coagulase-negative hemolytic staphylococcus albus was cultured from the blood and found *in vitro* to be markedly resistant to penicillin, slightly sensitive to streptomycin and markedly sensitive to aureomycin. Aureomycin was prescribed on the fifteenth hospital day in a dose of 500 mg. every four hours for twenty-four hours and 250 mg. every four hours thereafter. The temperature promptly returned to normal but on the twenty-first day she had a chill, rise in temperature and petechiae were found on the right conjunctiva. The aureomycin was increased to 500 mg. every four hours. The temperature returned to normal, five blood cultures were sterile and she was discharged on the forty-fifth hospital day to the Children's Heart Hospital, Philadelphia. There she was given 250 mg. aureomycin every four hours for three additional weeks. Six blood cultures in the next two months were sterile; she was afebrile.

In February, 1950, she was sent to the Philadelphia General Hospital for study because of a rising sedimentation rate. Blood cultures were repeatedly sterile, and she was thought to have had a reactivation of her rheumatic fever which had responded to bed rest and salicylates.

At this writing ten months have elapsed since treatment. Repeated blood cultures have been sterile, she has remained afebrile, the diastolic murmur has disappeared and the sedimentation rate is 48 mm. in one hour.

Case II. A sixty-nine year old white female was admitted November 27, 1949, to Presbyterian Hospital with the chief complaint of recurrent fever. The patient had no history of cardiac disease. She had pneumonia in August, 1949, which was followed by a persistent cough, low grade fever, tachycardia and intermittent left abdominal pain. She had lost 27 pounds and was becoming progressively weaker. Prior to admission she had received 15 million units of penicillin over twenty-five days, then 8 gm. of aureomycin during the next fifteen days, each of which had produced a temporary fall of temperature to normal.

Physical examination on admission revealed blood pressure 120/50, pulse 88. A blowing grade III systolic murmur was heard at the apex and transmitted to the axilla. The spleen was not palpable and no petechiae were noted. Pertinent laboratory findings were hemoglobin 10 gm., 72 per cent, red blood count 3.5 million, leukocyte count 5.3 thousand with 50 per cent filamented neutrophils, 16 per cent non-filamented neutrophils and 30 per cent lymphocytes. The sedimentation rate (Westergren) was 59 mm. in one hour. Three positive blood cultures were obtained for Streptococcus viridans. *In vitro* the organism was markedly resistant to penicillin, streptomycin and slightly sensitive to aureomycin. During the first seven days the temperature rose sharply in the evenings to as high as 103°F. Aureomycin was prescribed on the seventh day with an initial dose of 500 mg. followed by 250 mg. every eight hours. The temperature returned to normal until the seventeenth day when it reached 102°F. and a petechia was seen on her palate. Aureomycin was increased to 500 mg. every six hours. The temperature gradually returned to normal and remained so. The sedimentation rate dropped to 14 mm. in one hour. The murmur diminished in intensity. Three subsequent blood cultures were sterile and she was discharged on the forty-fourth day. Aureomycin was continued over forty-five days in a total dose of 18 gm. Seven months have since elapsed, the patient has gained weight, has been afebrile and the murmur has practically disappeared.

Case III. A sixteen year old white female was admitted to Presbyterian Hospital on May 3, 1950, for study. The patient was born with a congenital heart lesion but had no manifestation

other than a murmur. She had gained weight and developed normally, and school health authorities had reported the murmur without any other defects. Her activities had been somewhat limited by her family doctor. Two months prior to admission she noted excessive fatigue and weight loss. Three weeks previous to admission she began having a daily rise in temperature to about 102°F. associated with a chilly sensation. She was treated for pneumonia with unknown amounts of penicillin and aureomycin.

On admission her blood pressure was 130/65, pulse 120 and temperature 101°F. She appeared pale and showed signs of recent weight loss. There were rales and dullness to percussion present at the right lung base. Examination of the heart revealed no enlargement. A machinery murmur was heard loudest over the pulmonic area but transmitted over the entire upper chest. The spleen was not palpable and no petechiae were noted. Laboratory data included a red blood count of 4.5 million with 12 gm. hemoglobin. White blood count was 7.1 thousand with 51 per cent filamented and 22 per cent non-filamented neutrophils. Sedimentation rate (Westergren) was 91 mm. in one hour. Urinalysis was normal. Multiple agglutinations were negative. Chest x-ray showed enlargement of the pulmonary artery with no definite evidence of patent ductus or pulmonary stenosis. Bilateral basal bronchopneumonia was present. Electrocardiogram was interpreted as acute cor pulmonale with toxic myocardial changes.

Her temperature fluctuated from 100°F. to 104°F. and her symptoms persisted. On the fourth hospital day Str. viridans was isolated from the blood. The organism *in vitro* was resistant to penicillin, moderately sensitive to streptomycin and markedly sensitive to aureomycin which was prescribed in a dose of 1.5 gm. a day. She began feeling better and her temperature returned to normal. On the twentieth hospital day her chest x-ray showed almost complete clearing of the pneumonic process and the sedimentation rate had dropped to 26 mm. in one hour. On the twenty-first hospital day ligation of the patent ductus arteriosus was performed and the convalescence was uneventful. Aureomycin was continued postoperatively in a dose of 3 gm. a day for two weeks. She was discharged on the thirty-fifth hospital day. Since that time two blood cultures have been sterile, she has gained weight and remained afebrile.

COMMENTS

In case 1 the organism, usually susceptible to penicillin, became markedly resistant and the patient relapsed despite large doses of penicillin. In the second case the organism *in vitro* was only slightly sensitive to aureomycin but the clinical and bacteriologic response was excellent. The third case is difficult to evaluate in that frequently ligation alone is adequate therapy. However, the patient did so well pre- and postoperatively that I believe the aureomycin could well have been a contributing factor. No toxic reactions to aureomycin were noted except moderate initial nausea.

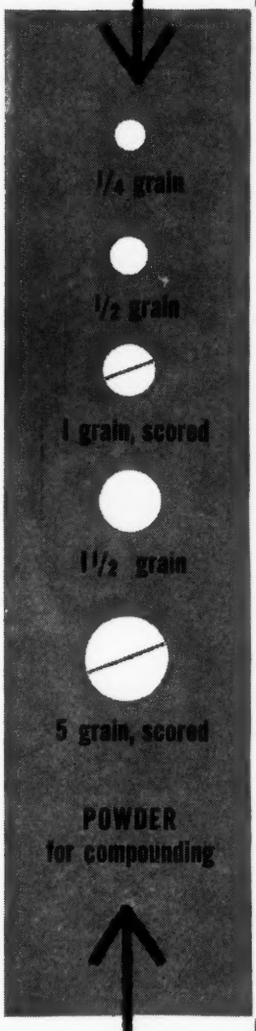
SUMMARY

Three cases of patients with subacute bacterial endocarditis successfully treated with aureomycin have been presented. All patients had been previously treated with penicillin and the gram-positive organisms were markedly resistant to penicillin.

REFERENCES

1. Long, P. H., Schoenbach, E. B., Bliss, E. A., Bryer, M. S. and Chandler, C. A. The experimental and clinical use of polymyxin, chloromycetin and aureomycin. *California Med.*, 70: 157, 1949.
2. Brainerd, H. D. What's new in aureomycin and other antibiotics. *California Med.*, 71: 9, 1949.
3. Harvey, J. C., Mirick, G. S. and Schaub, I. G. Clinical experience with aureomycin. *J. Clin. Investigation*, 28: 987, 1949.
4. Dowling, H. F., Lepper, M. H., Caldwell, E. R., Jr., Whelton, R. L. and Brickhouse, R. L. Aureomycin in various infections. *M. Ann. District Columbia*, 18: 335, 1949.
5. Astler, V. B. and Morgan, H. R. Some biologic complications of the prophylactic and therapeutic use of antibiotics. *Univ. Mich. M. Bull.*, 16: 127, 1950.
6. Allen, A. W. and Riecher, H. H. Bacterial endocarditis caused by a hemolytic staphylococcus albus. *J. Michigan M. Soc.*, 48: 1461, 1949.
7. Clinico-pathologic Conference. Penicillin-resistant subacute bacterial endocarditis. *Am. J. Med.*, 8: 794, 1950.

this is **Proloid** *the "pre-tested" thyroid*



To assure unvarying metabolism-stimulating effect, Proloid is pretested by BMR determinations in animals. Potency variations are eliminated *before*—not manifested *after* administration to the patient.

To spare the patient:

Rigid potency standardization of Proloid rules out metabolic fluctuations which might otherwise cause

the one extreme of jitteriness, tachycardia and nervousness due to unwitting overdosage

or the other extreme of recurrent hypothyroidism due to unwitting underdosage.

Proloid is highly purified:

Unlike ordinary whole-gland desiccated thyroid, Proloid is highly purified thyroglobulin. It is carefully freed of fat and extraneous organic matter but retains full metabolic potency.

Proloid is double-assayed:

Proloid is *chemically assayed* to conform to U.S.P. standard of 0.2% iodine—and *biologically assayed* in test animals to assure constant metabolic effects.

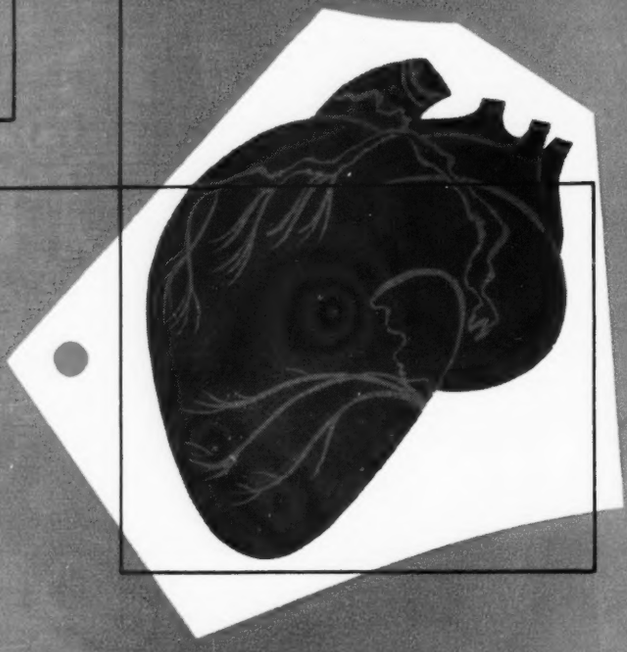
Proloid is prescribed in the same dosage as ordinary thyroid.

in **5** *tablet sizes and in powder*

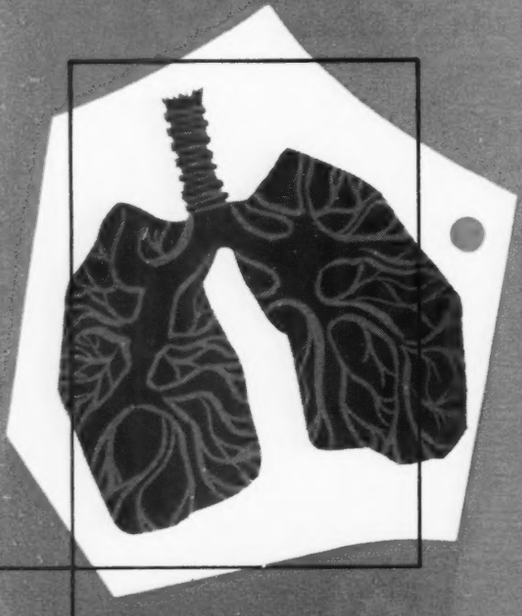
CHILCOTT
Laboratories DIVISION OF The Maltine Company
MORRIS PLAINS, NEW JERSEY

SPECIFICALLY . . .

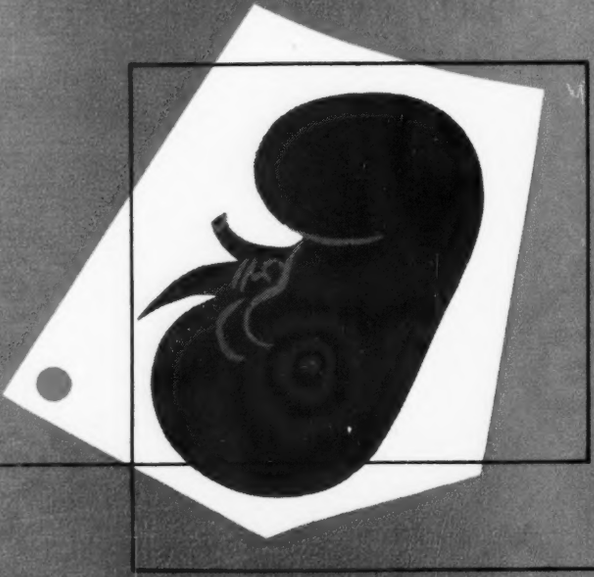
IN RHEUMATOID ARTHRITIS



IN RHEUMATIC FEVER



IN BRONCHIAL ASTHMA AND OTHER HYPERSENSITIVITIES



IN THE NEPHROTIC SYNDROME

PHYSIOLOGIC

Administration of ACTHAR initiates a chain of physiologic mechanisms in the service of preventing or correcting fundamental manifestations of disease.

ACTHAR, the specific pituitary stimulant hormone for the adrenal cortex, causes the adrenal glands to synthesize and secrete the entire spectrum of corticoids. These powerful physiologic agents control the mobilization and utilization of energy, inhibit cellular injury, and prevent or reverse the concomitant inflammatory reaction—a basic manifestation common to a wide variety of diseases.

Established Indications: Collagen diseases or connective tissue diseases, such as rheumatoid arthritis, rheumatic fever, acute lupus erythematosus; hypersensitivities, such as severe asthma, drug sensitivities, contact dermatitis; most acute inflammatory diseases of the eye; acute inflammatory conditions of the skin, such as acute pemphigus and exfoliative dermatitis; inflammatory conditions of the intestinal mucosa, such as ulcerative colitis; and metabolic diseases, such as acute gouty arthritis and secondary adrenal cortical hypofunction.

Literature and directions for administration of ACTHAR, including contraindications, available on request.

ACTHAR is available in 10, 15, 25 and 40 milligram vials.

ACTHAR

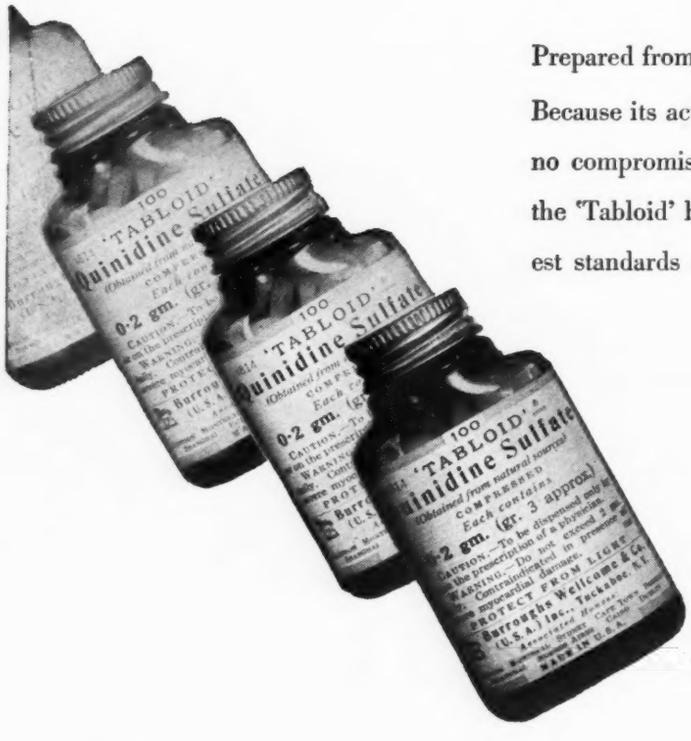
ARMOUR LABORATORIES BRAND OF ADRENOCORTICOTROPIC HORMONE (A. C. T. H.)

THE ARMOUR LABORATORIES

CHICAGO 11, ILLINOIS

PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

'TABLOID' ® brand QUINIDINE SULFATE 0.2 Gm. (gr.3)



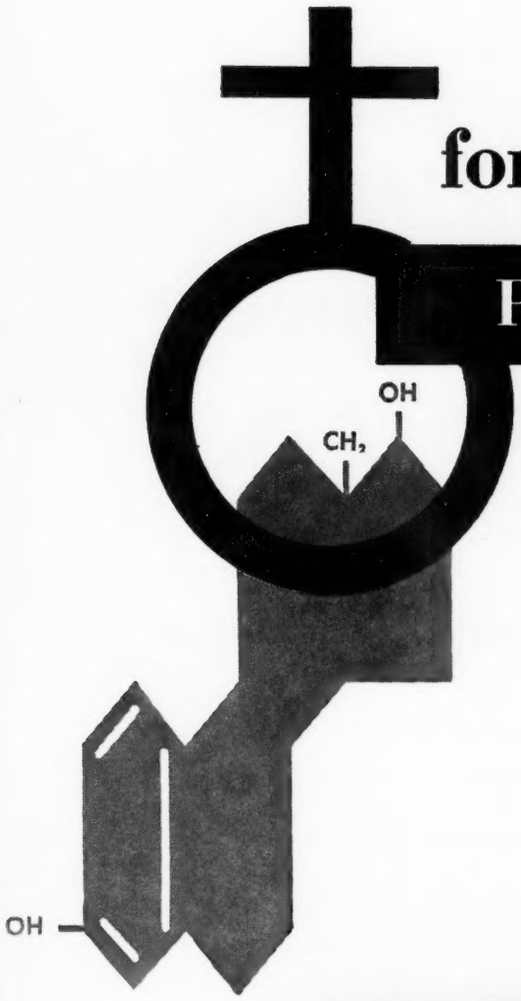
Prepared from **NATURAL** quinidine.

Because its action is so often vital there must be no compromise with the quality of quinidine—the 'Tabloid' brand product is made to the highest standards of purity, accuracy and reliability.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., TUCKAHOE 7, NEW YORK

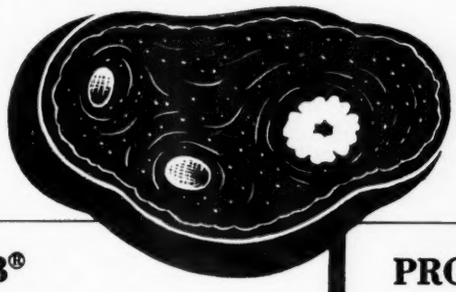
for estrogen therapy

PROGYNON®



the true, natural estrogenic hormone

When the menopause necessitates substitution therapy, quicker, more certain benefit without side effects will be obtained by administering and prescribing the PROGYNON preparations of estradiol, the hormone elaborated by the human ovary.

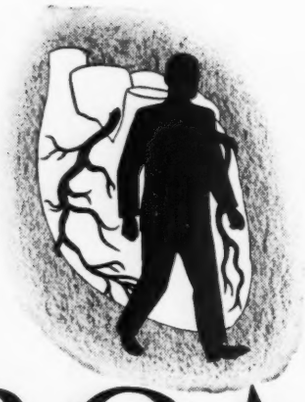


PROGYNON-B®	**PROGYNON *pellets***
PROGYNON *buccal tablets*	**PROGYNON *tablets***
PROGYNON-DP®	**PROGYNON-DH® *ointment***
PROGYNON, MICROPELLETS®	**PROGYNON-DH *suppositories***

PROGYNON

SCHERING

Schering CORPORATION·BLOOMFIELD, NEW JERSEY



a most significant advance

TROMEXAN T. M.

ethyl acetate

new, safer, oral anticoagulant

Throughout the exhaustive studies on TROMEXAN, involving many hundreds of cases, this new anticoagulant has proved singularly free from the dangers of hemorrhagic complication. Other advantageous clinical features of TROMEXAN are:

1 ***more rapid therapeutic response***
(therapeutic prothrombin level in 18-24 hours);

2 ***smooth, even maintenance of prothrombin level***
within therapeutic limits;

3 ***more rapid return to normal***
(24-48 hours) after cessation of administration.

In medical and surgical practice . . . as a prophylactic as well as a therapeutic agent . . . TROMEXAN extends the scope of anticoagulant treatment by reducing its hazards.

Detailed Brochure Sent on Request.

TROMEXAN (brand of ethyl biscoumacetate): available as uncoated scored tablets, 300 mg., bottles of 50 and 250.

Geigy

GEIGY COMPANY, INC.
Pharmaceutical Division, 89-91 Barclay St., New York 8, N. Y.

a practical *step forward* in the therapy of rheumatic affections

Pabalate usually provides better therapy for rheumatic affections than pure salicylate itself, through its mutually synergistic combination of para-aminobenzoic acid and salicylate.[1,2] Reports of authoritative clinical tests show a *higher* degree of pain relief... to *more* patients... on *lower* dosage... over *longer* periods... with *greater freedom* from adverse reactions.[3]

REFERENCES: 1. Dry, T. J. et al.: Proc. Staff Meetings Mayo Clin., 21:497, 1946. 2. Hoagland, R. J.: Am. J. Med., 9:272, 1950. 3. Smith, R. T.: J. Lancet, 70:192, 1950.

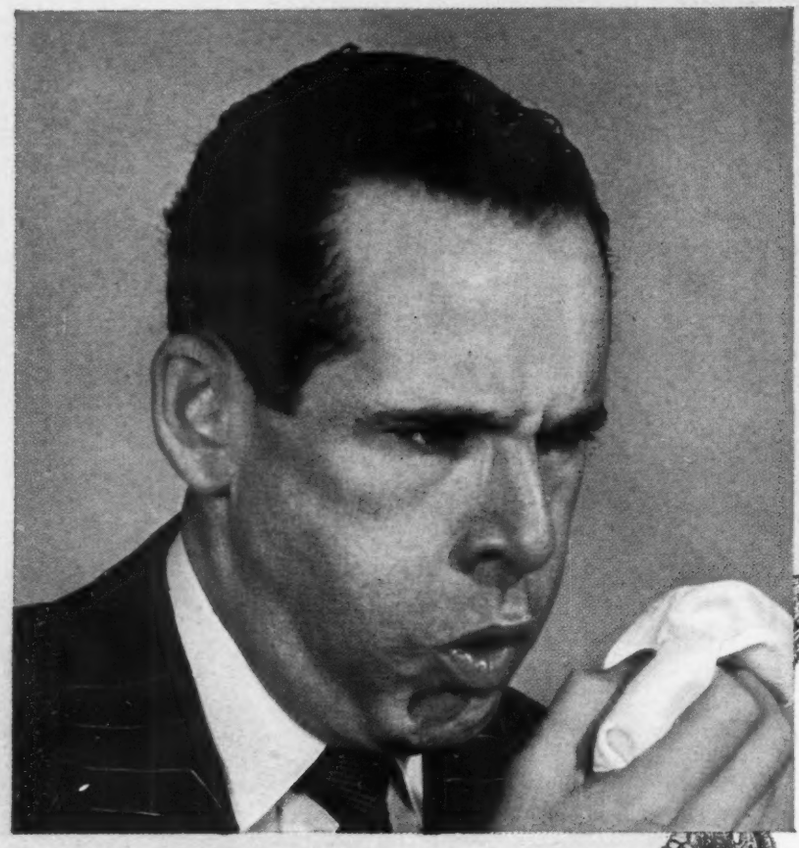
FORMULA: Each enteric-coated tablet or each teaspoonful of chocolate-flavored liquid contains 0.3 Gm. (5 gr.) sodium salicylate U.S.P., and 0.3 Gm. (5 gr.) para-aminobenzoic acid (as the sodium salt).

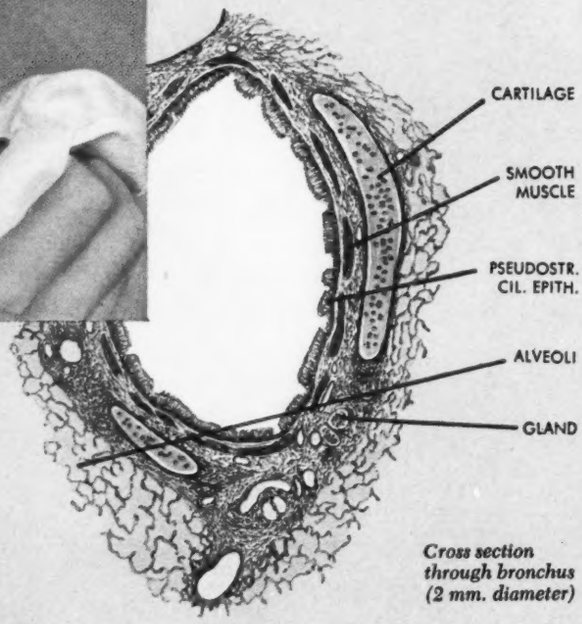
A. H. ROBINS CO., INC.
RICHMOND 20, VA.

Robins **Pabalate®**

Seven Years' Research that opened a **New Era**

in Cough Therapy





Cross section through bronchus (2 mm. diameter)

The time encrusted *empirical* approach to cough therapy—with its "picture of confusion, contradiction and neglect"[2]—can now be replaced by sound, *rational* non-narcotic treatment, thanks to the pioneering studies of Boyd et al.,[1,2] demonstrating that glyceryl guaiacolate is the most powerful of expectorants commonly used. Robitussin—the antitussive-expectorant with specific drug action—provides glyceryl guaiacolate for increasing respiratory tract fluid, together with desoxyephedrine, for its bronchial-spasm-relieving[3] and its mood-improving actions—in an aromatic syrup that is highly patient-acceptable.

A. H. ROBINS CO., INC. • RICHMOND 20, VA.

Robitussin®

A.H. Robins

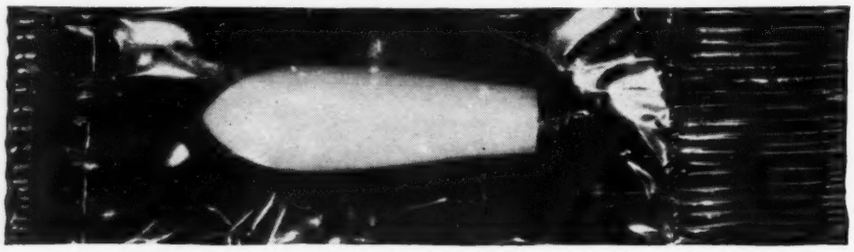
promotes useful cough... minimizes harmful cough

References:

1. Boyd, E. M. and Lapp, S.: J. Pharmacol. and Exper. Therap., 87:24, 1946. 2. Connell, W. F. et al.: Canad. M.A.J., 42:220, 1940. 3. Novelli, A. and Tainter, M. L.: J. Pharmacol., 77:324, 1943.

Formula:

Each 5 cc. (1 teaspoonful) contains 100 mg. glyceryl guaiacolate and 1 mg. desoxyephedrine hydrochloride, in a palatable aromatic syrup.



NUMOROIDAL SUPPOSITORIES

Soothing the Hemorrhoidal Area... Analgesic, vasoconstrictive medication in contact with the entire hemorrhoidal zone is provided in Numoroidal Suppositories. The special emulsifying base mixes with the secretions to assure coverage of the rectal area.

Convenient: Individually packed. No refrigeration necessary.

Formula: ephedrine hydrochloride 0.22%; benzocaine 5.00%, in a special emulsifying base. Average weight of 1 suppository—1.8 Gm.

Boxes of 12

NUMOTIZINE, Inc., 900 North Franklin Street, Chicago 10, Illinois

PERTENAL

treats more than the pressure in hypertension

...also controls harassing symptoms

Each PERTENAL tablet contains:

VERATRUM VIRIDE	100 mg.
HOMATROPINE METHYL BROMIDE	2.5 mg.
MANNITOL HEXANITRATE	30 mg.
PHENOBARBITAL	15 mg.

so that the *whole patient* feels better, more normal, more comfortable.

PERTENAL produces a... **substantial, sustained, safe descent in pressure** via dual hypotensive action... Heart load is eased.

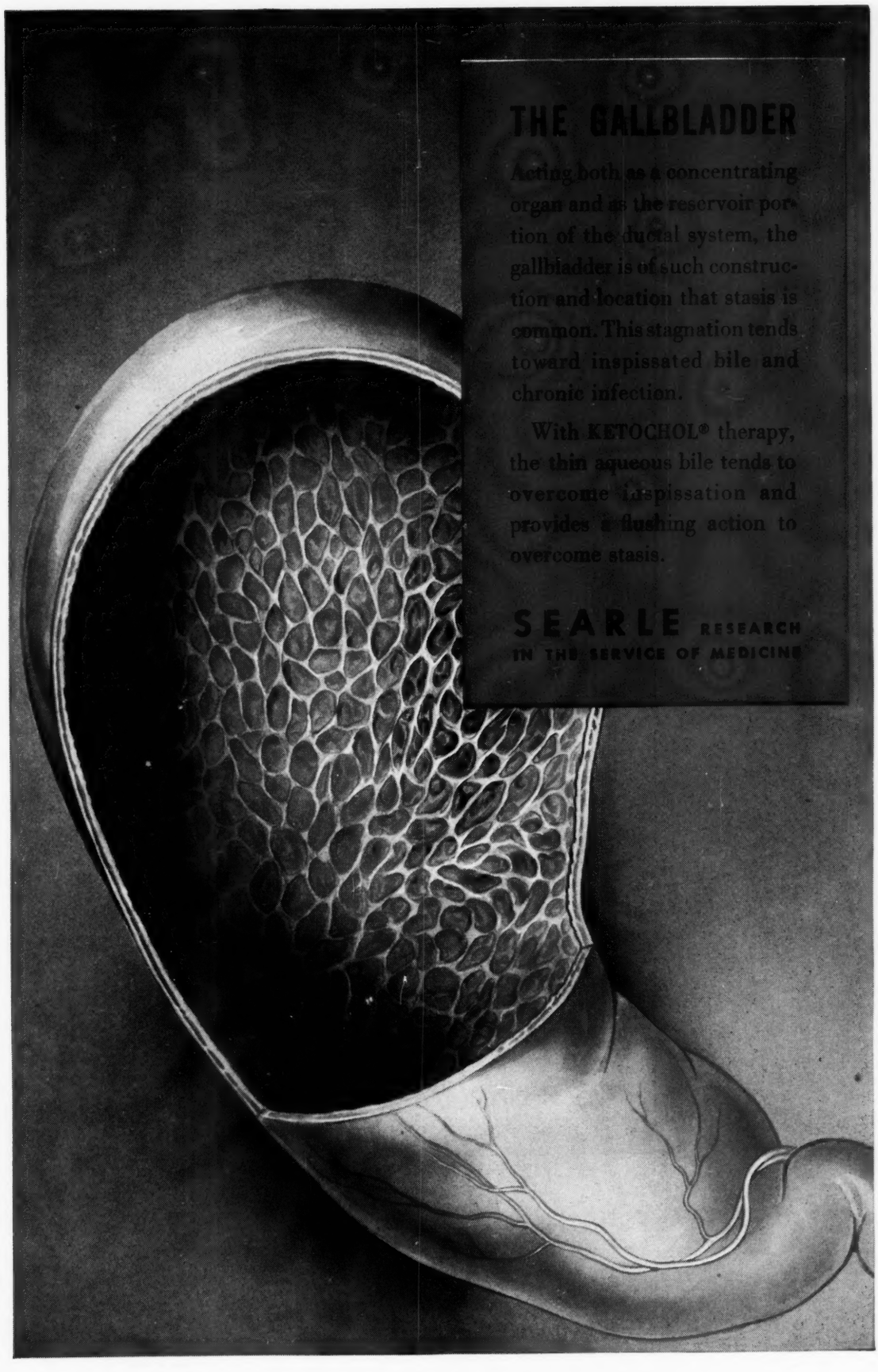
relaxes gastro-intestinal tension – relieving pain, spasm and other g.i. disturbances which may tend to aggravate hypertension.

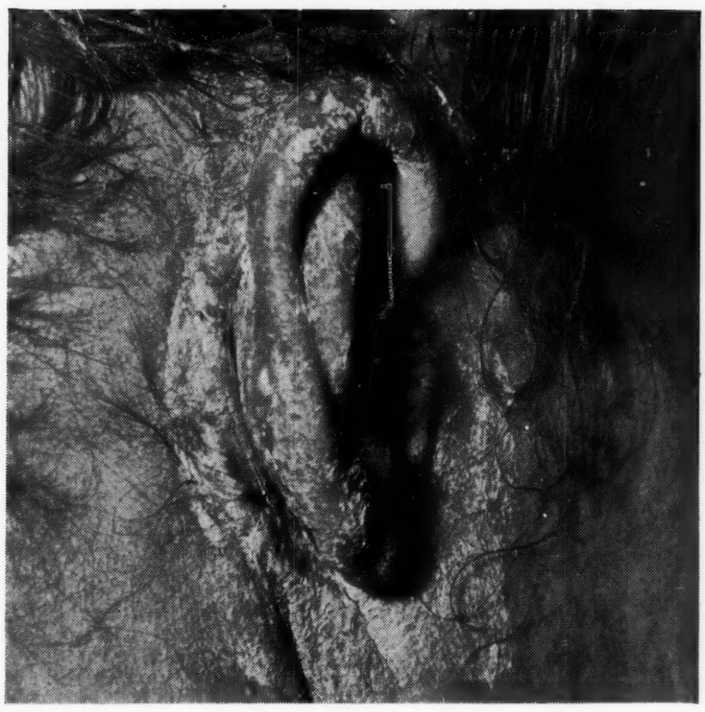
controls other symptoms that plague the hypertensive and send the pressure soaring – headache, nervousness, fear, insomnia, vertigo. Patients feel better as soon as PERTENAL therapy is started.

***write** for* **PERTENAL SAMPLES** *and literature.*

Crookes

CROOKES LABORATORIES, INC.
305 EAST 45 ST., NEW YORK, N.Y.


THE GALLBLADDER
Acting both as a concentrating organ and as the reservoir portion of the ductal system, the gallbladder is of such construction and location that stasis is common. This stagnation tends toward inspissated bile and chronic infection.
With KETOCHOL® therapy, the thin aqueous bile tends to overcome inspissation and provides a flushing action to overcome stasis.
SEARLE RESEARCH
IN THE SERVICE OF MEDICINE



Preferred therapy in seborrheic dermatitis

Pragmatar is generally recognized as the most effective preparation available for seborrheic dermatitis, and for the general care and hygiene of the seborrheic scalp. It is also extremely valuable in eczematous and psoriatic eruptions in which a seborrheic factor is involved.

Pragmatar incorporates—in a superior oil-in-water emulsion base—carefully balanced proportions of three of the drugs which are fundamental in dermatological practice. Pragmatar is non-gummy and non-staining; easy to apply and easy to remove.

PRAGMATAR

Highly effective in an unusually wide range of common skin disorders

Smith, Kline & French Laboratories, Philadelphia 'Pragmatar' T.M. Reg. U.S. Pat. Off.

FORMULA: Cetyl alcohol-coal tar distillate, 4%; near-colloidal sulfur, 3%; salicylic acid, 3%—incorporated in a special washable base.

White's

Dram-cillin with Triple Sulfonamides

- *wide spectrum of antibacterial action*
- *additive and possibly synergistic antibacterial potency*
- *markedly greater safety in systemic sulfonamide therapy*
- *apparent reduction in hypersensitive reactions*
- *less possibility of development of drug-resistant organisms*

excellent flavor, convenience and economy for the patient.

Each teaspoonful (5 cc.) supplies:

100,000 units buffered penicillin G potassium

.167 Gm. Sulfadiazine

.167 Gm. Sulfamerazine

.167 Gm. SULFACETIMIDE—the sulfonamide of choice for the *third* component

- *Supplied:* In 60 cc. bottles containing 1,200,000 units of penicillin G potassium and 6 Gm. of triple sulfonamide mixture.

WHITE LABORATORIES, INC.
Pharmaceutical Manufacturers, Newark 7, N. J.

When the diagnosis is Cystitis

First:

consider

ACCEPTED
COUNCIL ON PHARMACY AND CHEMISTRY
AMERICAN MEDICAL ASSOCIATION

to establish
and maintain
urinary antisepsis...

Four properties, in particular, make MANDELAMINE* a drug of choice whenever a diagnosis of urinary-tract infection has been made. MANDELAMINE has a wide therapeutic range, it retains its potency (even against organisms which have become resistant to other drugs), and it is relatively safe and simple to use.

Never are such properties more desirable than in the treatment of cystitis. It is therefore not surprising to find MANDELAMINE used widely, and with excellent results, in this disease (*cf.* Lowsley, O. S., and Kirwin, T. J.: Clinical Urology. Baltimore, The Williams and Wilkins Company, 1944; vol. 2, p. 1178).

MANDELAMINE is also indicated in pyelitis, prostatitis, nonspecific urethritis, and infections associated with urinary calculi or neurogenic bladder, as well as for pre- and postoperative prophylaxis in urologic surgery.

MANDELAMINE is available in bottles of 120, 500, and 1,000 enteric-coated tablets, through all prescription pharmacies. Literature and samples on request.

NEPERA

NEPERA CHEMICAL CO., INC.
Pharmaceutical Manufacturers
NEPERA PARK, YONKERS 2, N. Y.

*MANDELAMINE is the registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.

Advertiser Index

March 1951

10 clinical advantages

WITH JUST 2 DROPS .05% Privine

in decongestion

1. potent 2. prompt 3. prolonged 4. free from significant C.N.S. effects 5. few or no systemic effects 6. virtually non-allergenic 7. consonant with local physiologic function 8. non-irritating 9. safe 10. fosters patient cooperation.

Ciba SUMMIT, NEW JERSEY